



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/435, 31/40, C07D 207/26,</b> <b>413/06, 471/04, 401/06</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/30709</b>  <b>(43) International Publication Date:</b> 24 June 1999 (24.06.99)															
<b>(21) International Application Number:</b> PCT/US98/26539  <b>(22) International Filing Date:</b> 14 December 1998 (14.12.98)  <b>(30) Priority Data:</b> <table border="0"> <tr> <td>60/069,910</td> <td>17 December 1997 (17.12.97)</td> <td>US</td> </tr> <tr> <td>60/083,251</td> <td>27 April 1998 (27.04.98)</td> <td>US</td> </tr> <tr> <td>9810182.7</td> <td>13 May 1998 (13.05.98)</td> <td>GB</td> </tr> <tr> <td>9811283.2</td> <td>26 May 1998 (26.05.98)</td> <td>GB</td> </tr> <tr> <td>60/092,588</td> <td>13 July 1998 (13.07.98)</td> <td>US</td> </tr> </table> <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> DUGGAN, Mark, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MEISSNER, Robert, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PERKINS, James, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		60/069,910	17 December 1997 (17.12.97)	US	60/083,251	27 April 1998 (27.04.98)	US	9810182.7	13 May 1998 (13.05.98)	GB	9811283.2	26 May 1998 (26.05.98)	GB	60/092,588	13 July 1998 (13.07.98)	US	<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
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<b>(54) Title:</b> INTEGRIN RECEPTOR ANTAGONISTS  <b>(57) Abstract</b>  <p>The present invention relates to compounds and derivatives thereof, their synthesis, and their use as vitronectin receptor antagonists. More particularly, the compounds of the present invention are antagonists of the vitronectin receptors <math>\alpha v \beta 3</math> and/or <math>\alpha v \beta 5</math> and are useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, viral disease, and tumor growth.</p>																	

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<b>EE</b>	Estonia						

TITLE OF THE INVENTION  
INTEGRIN RECEPTOR ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

5                   The present invention is related to U.S. provisional applications Serial No. 60/069,910, filed December 17, 1997; 60/083,251, filed April 27, 1998; and 60/092,588, filed July 13, 1998; the contents of each of which are hereby incorporated by reference.

10   FIELD OF THE INVENTION

                  The present invention relates to compounds and derivatives thereof, their synthesis, and their use as integrin receptor antagonists. More particularly, the compounds of the present invention are antagonists of the integrin receptors  $\alpha v \beta 3$ ,  $\alpha v \beta 5$ , and/or  $\alpha v \beta 6$  and are  
15   useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, wound healing, viral disease, tumor growth, and metastasis.

20   BACKGROUND OF THE INVENTION

                  It is believed that a wide variety of disease states and conditions can be mediated by acting on integrin receptors and that integrin receptor antagonists represent a useful class of drugs. Integrin receptors are heterodimeric transmembrane receptors through which  
25   cells attach and communicate with extracellular matrices and other cells (See S.B. Rodan and G.A. Rodan, "Integrin Function In Osteoclasts", *Journal of Endocrinology*, Vol. 154, S47- S56 (1997), which is incorporated by reference herein in its entirety).

                  In one aspect of the present invention, the compounds  
30   herein are useful for inhibiting bone resorption. Bone resorption is mediated by the action of cells known as osteoclasts. Osteoclasts are large multinucleated cells of up to about 400  $\mu$ m in diameter that resorb mineralized tissue, chiefly calcium carbonate and calcium phosphate, in vertebrates. Osteoclasts are actively motile cells that migrate along  
35   the surface of bone, and can bind to bone, secrete necessary acids and

proteases, thereby causing the actual resorption of mineralized tissue from the bone. More specifically, osteoclasts are believed to exist in at least two physiological states, namely, the secretory state and the migratory or motile state. In the secretory state, osteoclasts are flat, attach to the bone matrix via a tight attachment zone (sealing zone), become highly polarized, form a ruffled border, and secrete lysosomal enzymes and protons to resorb bone. The adhesion of osteoclasts to bone surfaces is an important initial step in bone resorption. In the migratory or motile state, the osteoclasts migrate across bone matrix and do not take part in resorption until they again attach to bone.

Integrins are involved in osteoclast attachment, activation and migration. The most abundant integrin in osteoclasts, e.g., in rat, chicken, mouse and human osteoclasts, is an integrin receptor known as  $\alpha v \beta 3$ , which is thought to interact in bone with matrix proteins that contain the RGD sequence. Antibodies to  $\alpha v \beta 3$  block bone resorption *in vitro* indicating that this integrin plays a key role in the resorptive process. There is increasing evidence to suggest that  $\alpha v \beta 3$  ligands can be used effectively to inhibit osteoclast mediated bone resorption *in vivo* in mammals.

The current major bone diseases of public concern are osteoporosis, hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia, and glucocorticoid-induced osteoporosis. All of these conditions are characterized by bone loss, resulting from an imbalance between bone resorption, i.e. breakdown, and bone formation, which continues throughout life at the rate of about 14% per year on the average. However, the rate of bone turnover differs from site to site; for example, it is higher in the trabecular bone of the vertebrae and the alveolar bone in the jaws than in the cortices of the long bones. The potential for bone loss is directly related to turnover and can amount to over 5% per year in vertebrae immediately following menopause, a condition which leads to increased fracture risk.

In the United States, there are currently about 20 million people with detectable fractures of the vertebrae due to osteoporosis. In

addition, there are about 250,000 hip fractures per year attributed to osteoporosis. This clinical situation is associated with a 12% mortality rate within the first two years, while 30% of the patients require nursing home care after the fracture.

5           Individuals suffering from all the conditions listed above would benefit from treatment with agents which inhibit bone resorption.

          Additionally,  $\alpha v \beta 3$  ligands have been found to be useful in treating and/or inhibiting restenosis, i.e. recurrence of stenosis after corrective surgery on the heart valve, atherosclerosis, diabetic  
10   retinopathy, macular degeneration, and angiogenesis, i.e. formation of new blood vessels. Moreover, it has been postulated that the growth of tumors depends on an adequate blood supply, which in turn is dependent on the growth of new vessels into the tumor; thus, inhibition of angiogenesis can cause tumor regression in animal models (*See*  
15   Harrison's Principles of Internal Medicine, 12th ed., 1991, which is incorporated by reference herein in its entirety). Therefore,  $\alpha v \beta 3$  antagonists which inhibit angiogenesis can be useful in the treatment of cancer by inhibiting tumor growth (*See e.g., Brooks et al., Cell*, 79:1157-1164 (1994), which is incorporated by reference herein in its entirety).

20           Moreover, compounds of this invention can also inhibit neovascularization by acting as antagonists of the integrin receptor,  $\alpha v \beta 5$ . A monoclonal antibody for  $\alpha v \beta 5$  has been shown to inhibit VEGF-induced angiogenesis in rabbit cornea and the chick chorioallantoic membrane model (*See M.C. Friedlander, et al., Science* 270, 1500-1502,  
25   (1995), which is incorporated by reference herein in its entirety). Thus, compounds that antagonize  $\alpha v \beta 5$  are useful for treating and preventing macular degeneration, diabetic retinopathy, tumor growth, and metastasis.

          Additionally, compounds of the instant invention can  
30   inhibit angiogenesis and inflammation by acting as antagonists of the integrin receptor,  $\alpha v \beta 6$ , which is expressed during the later stages of wound healing and remains expressed until the wound is closed (*See Christofidou-Solomidou, et al., "Expression and Function of Endothelial Cell  $\alpha v$  Integrin Receptors in Wound-Induced Human Angiogenesis in*  
35   *Human Skin/SCID Mice Chimeras, American Journal of Pathology,*

Vol. 151, No. 4, pp. 975-983 (October 1997), which is incorporated by reference herein in its entirety). It is postulated that  $\alpha v \beta 6$  plays a role in the remodeling of the vasculature during the later stages of angiogenesis. Also,  $\alpha v \beta 6$  participates in the modulation of epithelial inflammation and is induced in response to local injury or  
5 inflammation (See Xiao-Zhu Huang, et al., "Inactivation of the Integrin  $\beta 6$  Subunit Gene Reveals a Role of Epithelial Integrins in Regulating Inflammation in the Lungs and Skin," Journal of Cell Biology, Vol. 133, No.4, pp. 921-928 (May 1996), which is incorporated by reference herein  
10 in its entirety). Accordingly, compounds that antagonize  $\alpha v \beta 6$  are useful in treating or preventing cancer by inhibiting tumor growth and metastasis.

In addition, certain compounds of this invention antagonize both the  $\alpha v \beta 3$  and  $\alpha v \beta 5$  receptors. These compounds, referred to as  
15 "dual  $\alpha v \beta 3 / \alpha v \beta 5$  antagonists," are useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, tumor growth, and metastasis.

In addition, certain compounds of this invention are useful  
20 as mixed  $\alpha v \beta 3$ ,  $\alpha v \beta 5$ , and  $\alpha v \beta 6$  receptor antagonists.

It is therefore an object of the present invention to provide compounds which are useful as integrin receptor antagonists.

It is another object of the present invention to provide compounds which are useful as  $\alpha v \beta 3$  receptor antagonists.

25 It is another object of the present invention to provide compounds which are useful as  $\alpha v \beta 5$  receptor antagonists.

It is another object of the present invention to provide compounds which are useful as  $\alpha v \beta 6$  receptor antagonists.

30 It is another object of the present invention to provide compounds which are useful as dual  $\alpha v \beta 3 / \alpha v \beta 5$  receptor antagonists.

It is another object of the present invention to provide compounds which are useful as mixed  $\alpha v \beta 3$ ,  $\alpha v \beta 5$ , and  $\alpha v \beta 6$  receptor antagonists.

35 It is another object of the present invention to provide pharmaceutical compositions comprising integrin receptor antagonists.

It is another object of the present invention to provide methods for making the pharmaceutical compositions of the present invention.

5 It is another object of the present invention to provide methods for eliciting an integrin receptor antagonizing effect in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

10 It is another object of the present invention to provide compounds and pharmaceutical compositions useful for inhibiting bone resorption, restenosis, atherosclerosis, inflammation, viral disease, diabetic retinopathy, macular degeneration, angiogenesis, tumor growth, and metastasis.

15 It is another object of the present invention to provide compounds and pharmaceutical compositions useful for treating osteoporosis.

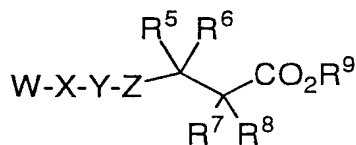
20 It is another object of the present invention to provide methods for inhibiting bone resorption, restenosis, atherosclerosis, inflammation, viral disease, diabetic retinopathy, macular degeneration, angiogenesis, tumor growth, and metastasis.

25 It is another object of the present invention to provide methods for treating osteoporosis.

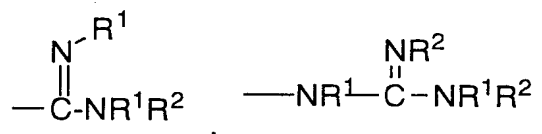
These and other objects will become readily apparent from the detailed description which follows.

## 25 SUMMARY OF THE INVENTION

The present invention relates to compounds of the formula



wherein W is selected from the group consisting of



5 a 5- or 6-membered monocyclic aromatic or nonaromatic ring system having 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S wherein the ring nitrogen atoms are unsubstituted or substituted with one R<sup>1</sup> substituent and the ring carbon atoms are unsubstituted or substituted with one or two R<sup>1</sup> substituents, and

10 a 9- to 14-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system has 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S, and wherein the ring nitrogen atoms are unsubstituted or substituted with one R<sup>1</sup> substituent and the ring carbon atoms are unsubstituted or substituted with one or two R<sup>1</sup> substituents;

X is selected from the group consisting of

20 -(CH<sub>2</sub>)<sub>v</sub>-, wherein any methylene (CH<sub>2</sub>) carbon atom is either unsubstituted or substituted with one or two R<sup>1</sup> substituents; and a 5- or 6-membered monocyclic aromatic or nonaromatic ring system having 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S wherein the ring nitrogen atoms are unsubstituted or substituted with one R<sup>1</sup> substituent and the ring carbon atoms are unsubstituted or substituted with one or two R<sup>1</sup> substituents;

Y is selected from the group consisting of

30 -(CH<sub>2</sub>)<sub>m</sub>-,  
 -(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>n</sub>-,  
 -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>4</sup>-(CH<sub>2</sub>)<sub>n</sub>-,  
 -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>n</sub>-,



- 5         $-(CH_2)_m-SO-(CH_2)_n-$ ,  
           $-(CH_2)_m-SO_2-(CH_2)_n-$ ,  
           $-(CH_2)_m-O-(CH_2)_n-O-(CH_2)_p-$ ,  
           $-(CH_2)_m-O-(CH_2)_n-NR^4-(CH_2)_p-$ ,  
           $-(CH_2)_m-NR^4-(CH_2)_n-NR^4-(CH_2)_p-$ ,  
           $-(CH_2)_m-O-(CH_2)_n-S-(CH_2)_p-$ ,  
           $-(CH_2)_m-S-(CH_2)_n-S-(CH_2)_p-$ ,  
           $-(CH_2)_m-NR^4-(CH_2)_n-S-(CH_2)_p-$ ,  
 10         $-(CH_2)_m-NR^4-(CH_2)_n-O-(CH_2)_p-$ ,  
           $-(CH_2)_m-S-(CH_2)_n-O-(CH_2)_p-$ , and  
           $-(CH_2)_m-S-(CH_2)_n-NR^4-(CH_2)_p-$ ,

wherein any methylene (CH<sub>2</sub>) carbon atom in Y, other than in R<sup>4</sup>, can be substituted by one or two R<sup>3</sup> substituents;

- 15        Z is a 5 membered aromatic or nonaromatic mono- or bicyclic ring system having 0 to 3 heteroatoms selected from the group consisting of N, O, and S, and wherein the ring system is either unsubstituted or substituted with 0, 1, 2, or 3 oxo or thio substituents, and either unsubstituted or substituted with one or more substituents  
 20        independently selected from the group consisting of R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> ;

wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of

- 25        hydrogen, halogen, C<sub>1-10</sub> alkyl, C<sub>3-8</sub> cycloalkyl,  
          C<sub>3-8</sub> cycloheteroalkyl, C<sub>3-8</sub> cycloalkyl C<sub>1-6</sub> alkyl,  
          C<sub>3-8</sub> cycloheteroalkyl C<sub>1-6</sub> alkyl, aryl, aryl C<sub>1-8</sub> alkyl, amino,  
          amino C<sub>1-8</sub> alkyl, C<sub>1-3</sub> acylamino, C<sub>1-3</sub> acylamino C<sub>1-8</sub> alkyl,  
          (C<sub>1-6</sub> alkyl)<sub>p</sub>amino, (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-8</sub> alkyl,  
          C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkoxy C<sub>1-6</sub> alkyl, hydroxycarbonyl,  
 30        hydroxycarbonyl C<sub>1-6</sub> alkyl, C<sub>1-3</sub> alkoxycarbonyl,  
          C<sub>1-3</sub> alkoxycarbonyl C<sub>1-6</sub> alkyl, hydroxycarbonyl-  
          C<sub>1-6</sub> alkyloxy, hydroxy, hydroxy C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxy-  
          C<sub>1-6</sub> alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy,  
          trifluoroethoxy, C<sub>1-8</sub> alkyl-S(O)<sub>p</sub>, (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,

C<sub>1-8</sub> alkyloxycarbonylamino, (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyloxy,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>amino, (aryl)<sub>p</sub>amino, aryl C<sub>1-8</sub>-  
 alkylsulfonylamino, and C<sub>1-8</sub> alkylsulfonylamino;  
 or two R<sup>1</sup> substituents, when on the same carbon atom, are taken  
 5 together with the carbon atom to which they are attached to  
 form a carbonyl group;

each R<sup>3</sup> is independently selected from the group consisting of  
 hydrogen,  
 10 aryl,  
 C<sub>1-10</sub> alkyl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 15 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 halogen,  
 hydroxyl,  
 20 oxo,  
 trifluoromethyl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxycarbonyl,  
 25 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 C<sub>1-6</sub> alkylcarbonyloxy,  
 C<sub>3-8</sub> cycloalkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 amino C<sub>1-6</sub> alkyl,  
 30 arylaminocarbonyl,  
 aryl C<sub>1-5</sub> alkylaminocarbonyl,  
 aminocarbonyl,  
 aminocarbonyl C<sub>1-6</sub> alkyl,  
 hydroxycarbonyl,

- hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 5 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 10 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkoxy,  
 15 aryl C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>amino,  
 (aryl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 20 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 arylcarbonyloxy,  
 aryl C<sub>1-6</sub> alkylcarbonyloxy,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>aminocarbonyloxy,  
 25 C<sub>1-8</sub> alkylsulfonylamino,  
 arylsulfonylamino,  
 C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
 arylsulfonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylsulfonylamino,  
 30 aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
 C<sub>1-8</sub> alkoxycarbonylamino,  
 C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
 aryloxy carbonylamino C<sub>1-8</sub> alkyl,  
 aryl C<sub>1-8</sub> alkoxycarbonylamino,

- aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonylamino,  
C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
arylcarbonylamino C<sub>1-6</sub> alkyl,  
5 aryl C<sub>1-6</sub> alkylcarbonylamino,  
aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
aminocarbonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
10 (aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
15 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylsulfonyl,  
20 C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
arylsulfonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonyl,  
aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylcarbonyl,  
25 C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
arylcarbonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonyl,  
aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylthiocarbonylamino,  
30 C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,

(aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl, and  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
or two R<sup>3</sup> substituents, when on the same carbon atom are taken  
5 together with the carbon atom to which they are attached to  
form a carbonyl group or a cyclopropyl group,  
wherein any of the alkyl groups of R<sup>3</sup> are either unsubstituted or  
substituted with one to three R<sup>1</sup> substituents,  
and provided that each R<sup>3</sup> is selected such that in the resultant  
10 compound the carbon atom or atoms to which R<sup>3</sup> is attached is itself  
attached to no more than one heteroatom;

each R<sup>4</sup> is independently selected from the group consisting of  
hydrogen,  
15 aryl,  
aminocarbonyl,  
C<sub>3-8</sub> cycloalkyl,  
amino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonyl,  
20 (aryl C<sub>1-5</sub> alkyl)<sub>p</sub>aminocarbonyl,  
hydroxycarbonyl C<sub>1-6</sub> alkyl,  
C<sub>1-8</sub> alkyl,  
aryl C<sub>1-6</sub> alkyl,  
(C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>2-6</sub> alkyl,  
25 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>2-6</sub> alkyl,  
C<sub>1-8</sub> alkylsulfonyl,  
C<sub>1-8</sub> alkoxycarbonyl,  
aryloxycarbonyl,  
aryl C<sub>1-8</sub> alkoxycarbonyl,  
30 C<sub>1-8</sub> alkylcarbonyl,  
arylcarbonyl,  
aryl C<sub>1-6</sub> alkylcarbonyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
aminosulfonyl,

- C<sub>1-8</sub> alkylaminosulfonyl,  
 (aryl)<sub>p</sub>aminosulfonyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonyl,  
 arylsulfonyl,  
 5 arylC<sub>1-6</sub> alkylsulfonyl,  
 C<sub>1-6</sub> alkylthiocarbonyl,  
 arylthiocarbonyl, and  
 aryl C<sub>1-6</sub> alkylthiocarbonyl,  
 wherein any of the alkyl groups of R<sup>4</sup> are either unsubstituted or  
 10 substituted with one to three R<sup>1</sup> substituents;
- R<sup>5</sup> and R<sup>6</sup> are each independently selected from the group consisting of  
 hydrogen;  
 C<sub>1-10</sub> alkyl,  
 15 aryl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 20 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 halogen,  
 hydroxyl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 25 aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxy carbonyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 C<sub>1-6</sub> alkylcarbonyloxy,  
 C<sub>3-8</sub> cycloalkyl,  
 30 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 amino C<sub>1-6</sub> alkyl,  
 arylaminocarbonyl,  
 aryl C<sub>1-5</sub> alkylaminocarbonyl,  
 aminocarbonyl,

- aminocarbonyl C<sub>1-6</sub> alkyl,  
 hydroxycarbonyl,  
 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 5 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 10 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 15 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 20 (aryl)<sub>p</sub>amino,  
 (aryl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 arylcarbonyloxy,  
 25 aryl C<sub>1-6</sub> alkylcarbonyloxy,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>aminocarbonyloxy,  
 C<sub>1-8</sub> alkylsulfonylamino,  
 arylsulfonylamino,  
 C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
 30 arylsulfonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylsulfonylamino,  
 aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
 C<sub>1-8</sub> alkoxycarbonylamino,  
 C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,

- aryloxycarbonylamino C<sub>1-8</sub> alkyl,  
aryl C<sub>1-8</sub> alkoxycarbonylamino,  
aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonylamino,  
5 C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
arylcarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonylamino,  
aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
aminocarbonylamino C<sub>1-6</sub> alkyl,  
10 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
15 aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
20 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylsulfonyl,  
C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
arylsulfonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonyl,  
25 aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylcarbonyl,  
C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
arylcarbonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonyl,  
30 aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylthiocarbonylamino,  
C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylthiocarbonylamino,



aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl, and  
 5 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl;

or R<sup>5</sup> and R<sup>6</sup> are taken together with the carbon atom to which they are  
 attached to form a carbonyl group,  
 wherein any of the alkyl groups of R<sup>5</sup> or R<sup>6</sup> are either unsubstituted or  
 substituted with one to three R<sup>1</sup> substituents, and provided that each R<sup>5</sup>  
 10 and R<sup>6</sup> are selected such that in the resultant compound the carbon  
 atom to which R<sup>5</sup> and R<sup>6</sup> are attached is itself attached to no more than  
 one heteroatom;

R<sup>7</sup> and R<sup>8</sup> are each independently selected from the group consisting of  
 15 hydrogen,  
 C<sub>1-10</sub> alkyl,  
 aryl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,  
 20 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 halogen,  
 25 hydroxyl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxycarbonyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 30 C<sub>1-6</sub> alkylcarbonyloxy,  
 C<sub>3-8</sub> cycloalkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 amino C<sub>1-6</sub> alkyl,  
 arylaminocarbonyl,

- aryl C<sub>1-5</sub> alkylaminocarbonyl,  
 aminocarbonyl,  
 aminocarbonyl C<sub>1-6</sub> alkyl,  
 hydroxycarbonyl,  
 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>amino,  
 (aryl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 arylcarbonyloxy,  
 aryl C<sub>1-6</sub> alkylcarbonyloxy,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>aminocarbonyloxy,  
 C<sub>1-8</sub> alkylsulfonylamino,  
 arylcarbonylamino,  
 arylsulfonylamino,  
 C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
 arylsulfonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylsulfonylamino,

- aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-8</sub> alkoxycarbonylamino,  
C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
aryloxycarbonylamino C<sub>1-8</sub> alkyl,  
5 aryl C<sub>1-8</sub> alkoxycarbonylamino,  
aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
arylcarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonylamino,  
10 aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
aminocarbonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
15 arylaminocarbonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
20 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylsulfonyl,  
25 C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
arylsulfonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonyl,  
aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylcarbonyl,  
30 C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
arylcarbonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonyl,  
aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylthiocarbonylamino,

- C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
5 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl, and  
C<sub>7-20</sub> polycyclyl C<sub>0-8</sub> alkylsulfonylamino;
- 10 wherein any of the alkyl groups of R<sup>7</sup> and R<sup>8</sup> are either unsubstituted or substituted with one to three R<sup>1</sup> substituents, and provided that each R<sup>7</sup> and R<sup>8</sup> are selected such that in the resultant compound the carbon atom to which R<sup>7</sup> and R<sup>8</sup> are attached is itself attached to no more than one heteroatom;
- 15 R<sup>9</sup> is selected from the group consisting of  
hydrogen,  
C<sub>1-8</sub> alkyl,  
aryl,  
20 aryl C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonyloxy C<sub>1-4</sub> alkyl,  
aryl C<sub>1-8</sub> alkylcarbonyloxy C<sub>1-4</sub> alkyl,  
C<sub>1-8</sub> alkylaminocarbonylmethylene, and  
C<sub>1-8</sub> dialkylaminocarbonylmethylene;
- 25 R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> are each independently selected from the group consisting of  
hydrogen,  
C<sub>1-8</sub> alkyl,  
30 aryl,  
halogen,  
hydroxyl,  
oxo,  
aminocarbonyl,

- C3-8 cycloalkyl,  
 amino C1-6 alkyl,  
 (aryl)<sub>p</sub>aminocarbonyl,  
 hydroxycarbonyl,  
 5 (aryl C1-5 alkyl)<sub>p</sub>aminocarbonyl,  
 hydroxycarbonyl C1-6 alkyl,  
 aryl C1-6 alkyl,  
 (C1-6 alkyl)<sub>p</sub>amino C1-6 alkyl,  
 (aryl C1-6 alkyl)<sub>p</sub>amino C2-6 alkyl,  
 10 C1-8 alkylsulfonyl,  
 C1-8 alkoxycarbonyl,  
 aryloxycarbonyl,  
 aryl C1-8 alkoxycarbonyl,  
 C1-8 alkylcarbonyl,  
 15 arylcarbonyl,  
 aryl C1-6 alkylcarbonyl,  
 (C1-8 alkyl)<sub>p</sub>aminocarbonyl,  
 aminosulfonyl,  
 C1-8 alkylaminosulfonyl,  
 20 (aryl)<sub>p</sub>aminosulfonyl,  
 (aryl C1-8 alkyl)<sub>p</sub>aminosulfonyl,  
 C1-6 alkylsulfonyl,  
 arylsulfonyl,  
 aryl C1-6 alkylsulfonyl,  
 25 aryl C1-6 alkylcarbonyl,  
 C1-6 alkylthiocarbonyl,  
 arylthiocarbonyl,  
 aryl C1-6 alkylthiocarbonyl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 30 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,

- $\text{HC}\equiv\text{C}-(\text{CH}_2)_t-$ ,  
 $\text{C}_{1-6} \text{ alkyl}-\text{C}\equiv\text{C}-(\text{CH}_2)_t-$ ,  
 $\text{C}_{3-7} \text{ cycloalkyl}-\text{C}\equiv\text{C}-(\text{CH}_2)_t-$ ,  
 $\text{aryl}-\text{C}\equiv\text{C}-(\text{CH}_2)_t-$ ,  
5  $\text{C}_{1-6} \text{ alkylaryl}-\text{C}\equiv\text{C}-(\text{CH}_2)_t-$ ,  
 $\text{CH}_2=\text{CH}-(\text{CH}_2)_t-$ ,  
 $\text{C}_{1-6} \text{ alkyl}-\text{CH}=\text{CH}-(\text{CH}_2)_t-$ ,  
 $\text{C}_{3-7} \text{ cycloalkyl}-\text{CH}=\text{CH}-(\text{CH}_2)_t-$ ,  
 $\text{aryl}-\text{CH}=\text{CH}-(\text{CH}_2)_t-$ ,  
10  $\text{C}_{1-6} \text{ alkylaryl}-\text{CH}=\text{CH}-(\text{CH}_2)_t-$ ,  
 $\text{C}_{1-6} \text{ alkyl}-\text{SO}_2-(\text{CH}_2)_t-$ ,  
 $\text{C}_{1-6} \text{ alkylaryl}-\text{SO}_2-(\text{CH}_2)_t-$ ,  
 $\text{C}_{1-8} \text{ alkylcarbonylamino}$ ,  
 $\text{aryl C}_{1-5} \text{ alkoxy}$ ,  
15  $\text{C}_{1-5} \text{ alkoxycarbonyl}$ ,  
 $(\text{C}_{1-8} \text{ alkyl})_p \text{ aminocarbonyl}$ ,  
 $\text{C}_{1-6} \text{ alkylcarbonyloxy}$ ,  
 $(\text{C}_{1-6} \text{ alkyl})_p \text{ amino}$ ,  
 $\text{aminocarbonyl C}_{1-6} \text{ alkyl}$ ,  
20  $\text{C}_{1-6} \text{ alkoxy}$ ,  
 $\text{aryl C}_{1-6} \text{ alkoxy}$ ,  
 $(\text{aryl})_p \text{ amino}$ ,  
 $(\text{aryl})_p \text{ amino C}_{1-6} \text{ alkyl}$ ,  
 $(\text{aryl C}_{1-6} \text{ alkyl})_p \text{ amino}$ ,  
25  $(\text{aryl C}_{1-6} \text{ alkyl})_p \text{ amino C}_{1-6} \text{ alkyl}$ ,  
 $\text{arylcarbonyloxy}$ ,  
 $\text{aryl C}_{1-6} \text{ alkylcarbonyloxy}$ ,  
 $(\text{C}_{1-6} \text{ alkyl})_p \text{ aminocarbonyloxy}$ ,  
 $\text{C}_{1-8} \text{ alkylsulfonylamino}$ ,  
30  $\text{arylsulfonylamino}$ ,  
 $\text{C}_{1-8} \text{ alkylsulfonylamino C}_{1-6} \text{ alkyl}$ ,  
 $\text{arylsulfonylamino C}_{1-6} \text{ alkyl}$ ,  
 $\text{aryl C}_{1-6} \text{ alkylsulfonylamino}$ ,  
 $\text{aryl C}_{1-6} \text{ alkylsulfonylamino C}_{1-6} \text{ alkyl}$ ,

- C<sub>1-8</sub> alkoxycarbonylamino,  
 C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
 aryloxycarbonylamino C<sub>1-8</sub> alkyl,  
 aryl C<sub>1-8</sub> alkoxycarbonylamino,  
 5 aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
 arylcarbonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylcarbonylamino,  
 10 aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
 aminocarbonylamino C<sub>1-6</sub> alkyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
 15 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
 aminosulfonylamino C<sub>1-6</sub> alkyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
 20 (aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylsulfonyl,  
 C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
 25 arylsulfonyl C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylsulfonyl,  
 aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylcarbonyl,  
 C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 30 arylcarbonyl C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylthiocarbonylamino,  
 C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,

arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
5 (aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl, and  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
wherein any of the alkyl groups of R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> are either  
unsubstituted or substituted with one to three R<sup>1</sup> substituents;

10

wherein

each m is independently an integer from 0 to 6;  
each n is independently an integer from 0 to 6  
each p is independently an integer from 0 to 2;  
15 each r is independently an integer from 1 to 3;  
each s is independently an integer from 0 to 3;  
each t is independently an integer from 0 to 3; and  
v is independently an integer from 0 to 6;

20 and the pharmaceutically acceptable salts thereof.

The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention and a pharmaceutically acceptable carrier.

25 The present invention also relates to methods for making the pharmaceutical compositions of the present invention.

The present invention also relates to methods for eliciting an integrin receptor antagonizing effect in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

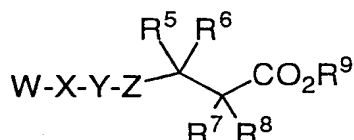
30 The present invention also relates to methods for inhibiting bone resorption, restenosis, atherosclerosis, inflammation, viral disease, diabetic retinopathy, macular degeneration, angiogenesis, wound healing, tumor growth, and metastasis by administering the compounds and pharmaceutical compositions of the present invention.



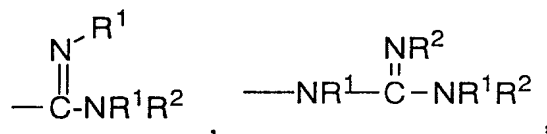
The present invention also relates to methods for treating osteoporosis by administering the compounds and pharmaceutical compositions of the present invention.

## 5 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds useful as integrin receptor antagonists. Representative compounds of the present invention are described by the following chemical formula:



10 wherein W is selected from the group consisting of



15 a 5- or 6-membered monocyclic aromatic or nonaromatic ring system having 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S wherein the ring nitrogen atoms are unsubstituted or substituted with one R<sup>1</sup> substituent and the ring carbon atoms are unsubstituted or substituted with one or two R<sup>1</sup> substituents, and

20 a 9- to 14-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system has 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S, and wherein the ring nitrogen atoms are unsubstituted or substituted with one R<sup>1</sup> substituent and the ring carbon atoms are unsubstituted or substituted with one or two R<sup>1</sup> substituents;

25

X is selected from the group consisting of

-(CH<sub>2</sub>)<sub>v</sub>-, wherein any methylene (CH<sub>2</sub>) carbon atom is either unsubstituted or substituted with one or two R<sup>1</sup> substituents;

5 and a 5- or 6-membered monocyclic aromatic or nonaromatic ring system having 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S wherein the ring nitrogen atoms are unsubstituted or substituted with one R<sup>1</sup> substituent and the ring carbon atoms are unsubstituted or substituted with one or two R<sup>1</sup> substituents;

10

Y is selected from the group consisting of

-(CH<sub>2</sub>)<sub>m</sub>-,  
 -(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>n</sub>-,  
 15 -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>4</sup>-(CH<sub>2</sub>)<sub>n</sub>-,  
 -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>n</sub>-,  
 -(CH<sub>2</sub>)<sub>m</sub>-SO-(CH<sub>2</sub>)<sub>n</sub>-,  
 -(CH<sub>2</sub>)<sub>m</sub>-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-,  
 -(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>p</sub>-,  
 20 -(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>n</sub>-NR<sup>4</sup>-(CH<sub>2</sub>)<sub>p</sub> -,  
 -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>4</sup>-(CH<sub>2</sub>)<sub>n</sub>-NR<sup>4</sup>-(CH<sub>2</sub>)<sub>p</sub> -,  
 -(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>n</sub>-S-(CH<sub>2</sub>)<sub>p</sub> -,  
 -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>n</sub>-S-(CH<sub>2</sub>)<sub>p</sub> -,  
 -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>4</sup>-(CH<sub>2</sub>)<sub>n</sub>-S-(CH<sub>2</sub>)<sub>p</sub> -,  
 25 -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>4</sup> -(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>p</sub> -,  
 -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>p</sub> -, and  
 -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>n</sub>-NR<sup>4</sup>-(CH<sub>2</sub>)<sub>p</sub> -,

wherein any methylene (CH<sub>2</sub>) carbon atom in Y, other than in R<sup>4</sup>, can  
 30 be substituted by one or two R<sup>3</sup> substituents;

Z is a 5 membered aromatic or nonaromatic mono- or bicyclic ring system having 0 to 3 heteroatoms selected from the group consisting of N, O, and S, and wherein the ring system is either unsubstituted or

substituted with 0, 1, 2, or 3 oxo or thio substituents, and either unsubstituted or substituted with one or more substituents independently selected from the group consisting of R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> ;

- 5 wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of
- hydrogen, halogen, C<sub>1-10</sub> alkyl, C<sub>3-8</sub> cycloalkyl,
  - C<sub>3-8</sub> cycloheteroalkyl, C<sub>3-8</sub> cycloalkyl C<sub>1-6</sub> alkyl,
  - C<sub>3-8</sub> cycloheteroalkyl C<sub>1-6</sub> alkyl, aryl, aryl C<sub>1-8</sub> alkyl, amino,
  - 10 amino C<sub>1-8</sub> alkyl, C<sub>1-3</sub> acylamino, C<sub>1-3</sub> acylamino C<sub>1-8</sub> alkyl,
  - (C<sub>1-6</sub> alkyl)<sub>p</sub>amino, (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-8</sub> alkyl,
  - C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkoxy C<sub>1-6</sub> alkyl, hydroxycarbonyl,
  - hydroxycarbonyl C<sub>1-6</sub> alkyl, C<sub>1-3</sub> alkoxycarbonyl,
  - C<sub>1-3</sub> alkoxycarbonyl C<sub>1-6</sub> alkyl, hydroxycarbonyl-
  - 15 C<sub>1-6</sub> alkyloxy, hydroxy, hydroxy C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxy-
  - C<sub>1-6</sub> alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy,
  - trifluoroethoxy, C<sub>1-8</sub> alkyl-S(O)<sub>p</sub>, (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,
  - C<sub>1-8</sub> alkyloxycarbonylamino, (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyloxy,
  - (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>amino, (aryl)<sub>p</sub>amino, aryl C<sub>1-8</sub>
  - 20 alkylsulfonamino, and C<sub>1-8</sub> alkylsulfonamino;
  - or two R<sup>1</sup> substituents, when on the same carbon atom, are taken together with the carbon atom to which they are attached to form a carbonyl group;
- 25 each R<sup>3</sup> is independently selected from the group consisting of
- hydrogen,
  - aryl,
  - C<sub>1-10</sub> alkyl,
  - aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,
  - 30 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,
  - aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,
  - aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,
  - aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,
  - aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,
  - 35 halogen,

hydroxyl,  
 oxo,  
 trifluoromethyl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 5 aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxycarbonyl,  
 (C<sub>1-8</sub> alkyl)paminocarbonyl,  
 C<sub>1-6</sub> alkylcarbonyloxy,  
 C<sub>3-8</sub> cycloalkyl,  
 10 (C<sub>1-6</sub> alkyl)pamino,  
 amino C<sub>1-6</sub> alkyl,  
 arylaminocarbonyl,  
 aryl C<sub>1-5</sub>-alkylaminocarbonyl,  
 aminocarbonyl,  
 15 aminocarbonyl C<sub>1-6</sub> alkyl,  
 hydroxycarbonyl,  
 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 20 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 25 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 30 C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkyl,  
 (C<sub>1-6</sub> alkyl)pamino C<sub>1-6</sub> alkyl,  
 (aryl)pamino,  
 35 (aryl)pamino C<sub>1-6</sub> alkyl,

- (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
(aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
arylcarbonyloxy,  
aryl C<sub>1-6</sub> alkylcarbonyloxy,  
5 (C<sub>1-6</sub> alkyl)<sub>p</sub>aminocarbonyloxy,  
C<sub>1-8</sub> alkylsulfonylamino,  
arylsulfonylamino,  
C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
arylsulfonylamino C<sub>1-6</sub> alkyl,  
10 aryl C<sub>1-6</sub> alkylsulfonylamino,  
aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-8</sub> alkoxycarbonylamino,  
C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
aryloxycarbonylamino C<sub>1-8</sub> alkyl,  
15 aryl C<sub>1-8</sub> alkoxycarbonylamino,  
aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonylamino,  
C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
arylcarbonylamino C<sub>1-6</sub> alkyl,  
20 aryl C<sub>1-6</sub> alkylcarbonylamino,  
aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
aminocarbonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
25 (aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
30 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylsulfonyl,

C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
arylsulfonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonyl,  
aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
5 C<sub>1-6</sub> alkylcarbonyl,  
C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
arylcarbonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonyl,  
aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
10 C<sub>1-6</sub> alkylthiocarbonylamino,  
C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
15 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl, and  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl;  
or two R<sup>3</sup> substituents, when on the same carbon atom are taken  
20 together with the carbon atom to which they are attached to  
form a carbonyl group or a cyclopropyl group,  
wherein any of the alkyl groups of R<sup>3</sup> are either unsubstituted or  
substituted with one to three R<sup>1</sup> substituents,  
and provided that each R<sup>3</sup> is selected such that in the resultant  
25 compound the carbon atom or atoms to which R<sup>3</sup> is attached is itself  
attached to no more than one heteroatom;

each R<sup>4</sup> is independently selected from the group consisting of  
hydrogen,  
30 aryl,  
aminocarbonyl,  
C<sub>3-8</sub> cycloalkyl,  
amino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonyl,

(aryl C<sub>1-5</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-8</sub> alkyl,  
 aryl C<sub>1-6</sub> alkyl,  
 5 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>2-6</sub> alkyl,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>2-6</sub> alkyl,  
 C<sub>1-8</sub> alkylsulfonyl,  
 C<sub>1-8</sub> alkoxycarbonyl,  
 aryloxycarbonyl,  
 10 aryl C<sub>1-8</sub> alkoxycarbonyl,  
 C<sub>1-8</sub> alkylcarbonyl,  
 arylcarbonyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 15 aminosulfonyl,  
 C<sub>1-8</sub> alkylaminosulfonyl,  
 (aryl)<sub>p</sub>aminosulfonyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonyl,  
 arylsulfonyl,  
 20 arylC<sub>1-6</sub> alkylsulfonyl,  
 C<sub>1-6</sub> alkylthiocarbonyl,  
 arylthiocarbonyl, and  
 aryl C<sub>1-6</sub> alkylthiocarbonyl,  
 wherein any of the alkyl groups of R<sup>4</sup> are either unsubstituted or  
 25 substituted with one to three R<sup>1</sup> substituents;

R<sup>5</sup> and R<sup>6</sup> are each independently selected from the group consisting of  
 hydrogen,  
 C<sub>1-10</sub> alkyl,  
 30 aryl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,

- aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 halogen,  
 hydroxyl,  
 5 C<sub>1-8</sub> alkylcarbonylamino,  
 aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxycarbonyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 C<sub>1-6</sub> alkylcarbonyloxy,  
 10 C<sub>3-8</sub> cycloalkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 amino C<sub>1-6</sub> alkyl,  
 arylaminocarbonyl,  
 aryl C<sub>1-5</sub> alkylaminocarbonyl,  
 15 aminocarbonyl,  
 aminocarbonyl C<sub>1-6</sub> alkyl,  
 hydroxycarbonyl,  
 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 20 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 25 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 30 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,



- (aryl)<sub>p</sub>amino,  
(aryl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
(aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
5 arylcarbonyloxy,  
aryl C<sub>1-6</sub> alkylcarbonyloxy,  
(C<sub>1-6</sub> alkyl)<sub>p</sub>aminocarbonyloxy,  
C<sub>1-8</sub> alkylsulfonylamino,  
arylsulfonylamino,  
10 C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
arylsulfonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonylamino,  
aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-8</sub> alkoxy carbonylamino,  
15 C<sub>1-8</sub> alkoxy carbonylamino C<sub>1-8</sub> alkyl,  
aryloxy carbonylamino C<sub>1-8</sub> alkyl,  
aryl C<sub>1-8</sub> alkoxy carbonylamino,  
aryl C<sub>1-8</sub> alkoxy carbonylamino C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonylamino,  
20 C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
arylcarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonylamino,  
aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
aminocarbonylamino C<sub>1-6</sub> alkyl,  
25 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
30 aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,

- (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylsulfonyl,  
 C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
 arylsulfonyl C<sub>1-6</sub> alkyl,  
 5 aryl C<sub>1-6</sub> alkylsulfonyl,  
 aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylcarbonyl,  
 C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 arylcarbonyl C<sub>1-6</sub> alkyl,  
 10 aryl C<sub>1-6</sub> alkylcarbonyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylthiocarbonylamino,  
 C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 15 aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl, and  
 20 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 or R<sup>5</sup> and R<sup>6</sup> are taken together with the carbon atom to which they are  
 attached to form a carbonyl group,  
 wherein any of the alkyl groups of R<sup>5</sup> or R<sup>6</sup> are either unsubstituted or  
 substituted with one to three R<sup>1</sup> substituents, and provided that each R<sup>5</sup>  
 25 and R<sup>6</sup> are selected such that in the resultant compound the carbon  
 atom to which R<sup>5</sup> and R<sup>6</sup> are attached is itself attached to no more than  
 one heteroatom;
- R<sup>7</sup> and R<sup>8</sup> are each independently selected from the group consisting of  
 30 hydrogen,  
 C<sub>1-10</sub> alkyl,  
 aryl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,

- aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 5 halogen,  
 hydroxyl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxy carbonyl,  
 10 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 C<sub>1-6</sub> alkylcarbonyloxy,  
 C<sub>3-8</sub> cycloalkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 amino C<sub>1-6</sub> alkyl,  
 15 arylaminocarbonyl,  
 aryl C<sub>1-5</sub> alkylaminocarbonyl,  
 aminocarbonyl,  
 aminocarbonyl C<sub>1-6</sub> alkyl,  
 hydroxycarbonyl,  
 20 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 25 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 30 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkoxy,

aryl C<sub>1-6</sub> alkyl,  
(C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>amino,  
(aryl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
5 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
(aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
arylcabonyloxy,  
aryl C<sub>1-6</sub> alkylcabonyloxy,  
(C<sub>1-6</sub> alkyl)<sub>p</sub>aminocabonyloxy,  
10 C<sub>1-8</sub> alkylsulfonylamino,  
arylsulfonylamino,  
C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
arylsulfonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonylamino,  
15 aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-8</sub> alkoxycarbonylamino,  
C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
aryloxcarbonylamino C<sub>1-8</sub> alkyl,  
aryl C<sub>1-8</sub> alkoxycarbonylamino,  
20 aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonylamino,  
C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
arylcabonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonylamino,  
25 aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
aminocabonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocabonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocabonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocabonylamino C<sub>1-6</sub> alkyl,  
30 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocabonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocabonylamino C<sub>1-6</sub> alkyl,  
aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,

- (aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylsulfonyl,  
 5 C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
 arylsulfonyl C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylsulfonyl,  
 aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylcarbonyl,  
 10 C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 arylcarbonyl C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylthiocarbonylamino,  
 15 C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 20 (aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl, and  
 C<sub>7-20</sub> polycyclyl C<sub>0-8</sub> alkylsulfonylamino;  
 wherein any of the alkyl groups of R<sup>7</sup> and R<sup>8</sup> are either unsubstituted or  
 25 substituted with one to three R<sup>1</sup> substituents, and provided that each  
 R<sup>7</sup> and R<sup>8</sup> are selected such that in the resultant compound the carbon  
 atom at which R<sup>7</sup> and R<sup>8</sup> are attached is itself attached to no more than  
 one heteroatom;
- 30 R<sup>9</sup> is selected from the group consisting of  
 hydrogen,  
 C<sub>1-8</sub> alkyl,  
 aryl,  
 aryl C<sub>1-8</sub> alkyl,

C<sub>1-8</sub> alkylcarbonyloxy C<sub>1-4</sub> alkyl,  
aryl C<sub>1-8</sub> alkylcarbonyloxy C<sub>1-4</sub> alkyl,  
C<sub>1-8</sub> alkylaminocarbonylmethylene, and  
C<sub>1-8</sub> dialkylaminocarbonylmethylene;

5

R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> are each independently selected from the group  
consisting of

hydrogen,  
C<sub>1-8</sub> alkyl,  
10 aryl,  
halogen,  
hydroxyl,  
oxo,  
aminocarbonyl,  
15 C<sub>3-8</sub> cycloalkyl,  
amino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonyl,  
hydroxycarbonyl,  
(aryl C<sub>1-5</sub> alkyl)<sub>p</sub>aminocarbonyl,  
20 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkyl,  
(C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>2-6</sub> alkyl,  
C<sub>1-8</sub> alkylsulfonyl,  
25 C<sub>1-8</sub> alkoxycarbonyl,  
aryloxycarbonyl,  
aryl C<sub>1-8</sub> alkoxycarbonyl,  
C<sub>1-8</sub> alkylcarbonyl,  
arylcarbonyl,  
30 aryl C<sub>1-6</sub> alkylcarbonyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
aminosulfonyl,  
C<sub>1-8</sub> alkylaminosulfonyl,  
(aryl)<sub>p</sub>aminosulfonyl,

- (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonyl,  
 C<sub>1-6</sub> alkylsulfonyl,  
 arylsulfonyl,  
 aryl C<sub>1-6</sub> alkylsulfonyl,  
 5 aryl C<sub>1-6</sub> alkylcarbonyl,  
 C<sub>1-6</sub> alkylthiocarbonyl,  
 arylthiocarbonyl,  
 aryl C<sub>1-6</sub> alkylthiocarbonyl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 10 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 15 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 20 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 25 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxycarbonyl,  
 30 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 C<sub>1-6</sub> alkylcarbonyloxy,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 aminocarbonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkoxy,

- aryl C<sub>1-6</sub> alkoxy,  
(aryl)<sub>p</sub>amino,  
(aryl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
5 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
arylcabonyloxy,  
aryl C<sub>1-6</sub> alkylcabonyloxy,  
(C<sub>1-6</sub> alkyl)<sub>p</sub>aminocabonyloxy,  
C<sub>1-8</sub> alkylsulfonylamino,  
10 arylsulfonylamino,  
C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
arylsulfonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonylamino,  
aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
15 C<sub>1-8</sub> alkoxycabonylamino,  
C<sub>1-8</sub> alkoxycabonylamino C<sub>1-8</sub> alkyl,  
aryloxycabonylamino C<sub>1-8</sub> alkyl,  
aryl C<sub>1-8</sub> alkoxycabonylamino,  
aryl C<sub>1-8</sub> alkoxycabonylamino C<sub>1-8</sub> alkyl,  
20 C<sub>1-8</sub> alkylcabonylamino,  
C<sub>1-8</sub> alkylcabonylamino C<sub>1-6</sub> alkyl,  
arylcabonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcabonylamino,  
aryl C<sub>1-6</sub> alkylcabonylamino C<sub>1-6</sub> alkyl,  
25 aminocabonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocabonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocabonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocabonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocabonylamino,  
30 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocabonylamino C<sub>1-6</sub> alkyl,  
aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,



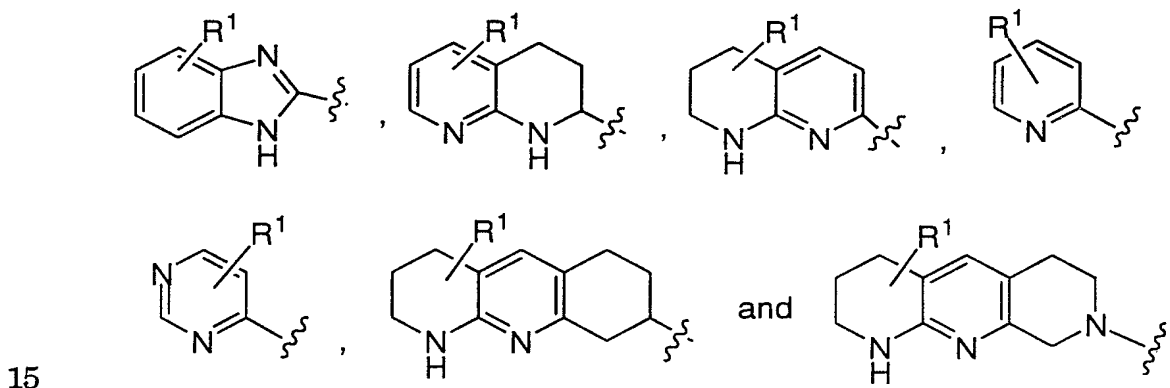
- (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylsulfonyl,  
 C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
 5 arylsulfonyl C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylsulfonyl,  
 aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylcarbonyl,  
 C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 10 arylcarbonyl C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylthiocarbonylamino,  
 C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 15 arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 20 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl, and  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,
- wherein any of the alkyl groups of R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> are either unsubstituted or substituted with one to three R<sup>1</sup> substituents;
- 25 wherein  
 each m is independently an integer from 0 to 6;  
 each n is independently an integer from 0 to 6  
 each p is independently an integer from 0 to 2;  
 each r is independently an integer from 1 to 3;  
 30 each s is independently an integer from 0 to 3;  
 each t is independently an integer from 0 to 3; and  
 v is independently an integer from 0 to 6;

and the pharmaceutically acceptable salts thereof.

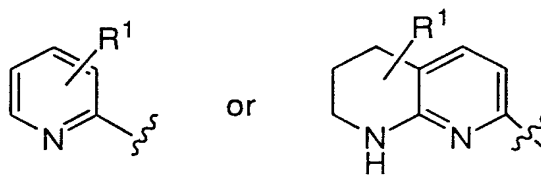
In the compounds of the present invention, W is preferably a 6-membered monocyclic aromatic or nonaromatic ring system having 1 or 2 nitrogen atoms wherein each carbon atom is either unsubstituted or substituted with one R<sup>1</sup> substituent, or

a 9- to 14-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system has 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S wherein the ring nitrogen atoms are unsubstituted or substituted with one R<sup>1</sup> substituent and the ring carbon atoms are unsubstituted or substituted with one or two R<sup>1</sup> substituents.

More preferably, W is selected from the group consisting of



Most preferably W is



In the compounds of the present invention, X is preferably -(CH<sub>2</sub>)<sub>v</sub>-, wherein any methylene (CH<sub>2</sub>) carbon atom is either unsubstituted or substituted with one or two R<sup>1</sup> substituents.

More preferably X is a direct bond, that is, v is 0.

In the compounds of the present invention, Y is preferably selected from the group consisting of

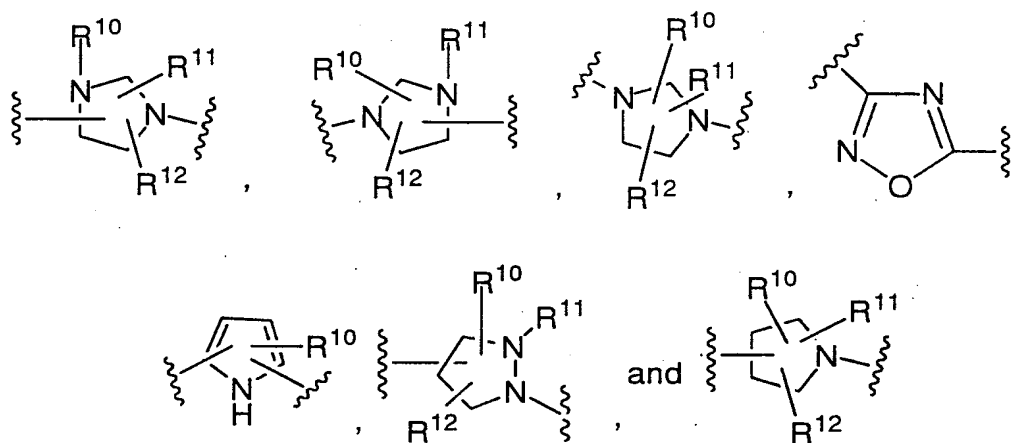
- 5            $-(CH_2)_m-$ ,  
               $-(CH_2)_m-O-(CH_2)_n-$ ,  
               $-(CH_2)_m-NR^4-(CH_2)_n-$ ,  
               $-(CH_2)_m-S-(CH_2)_n-$ ,  
               $-(CH_2)_m-SO-(CH_2)_n-$ ,  
 10            $-(CH_2)_m-SO_2-(CH_2)_n-$ ,  
               $-(CH_2)_m-O-(CH_2)_n-O-(CH_2)_p-$ ,  
               $-(CH_2)_m-O-(CH_2)_n-NR^4-(CH_2)_p-$ ,  
               $-(CH_2)_m-NR^4-(CH_2)_n-NR^4-(CH_2)_p-$ , and  
               $-(CH_2)_m-NR^4-(CH_2)_n-O-(CH_2)_p-$ ,  
 15       wherein any carbon atom in Y, other than in  $R^4$ , can be substituted by  
          one or two  $R^3$  substituents.

More preferably Y is selected from the group consisting of

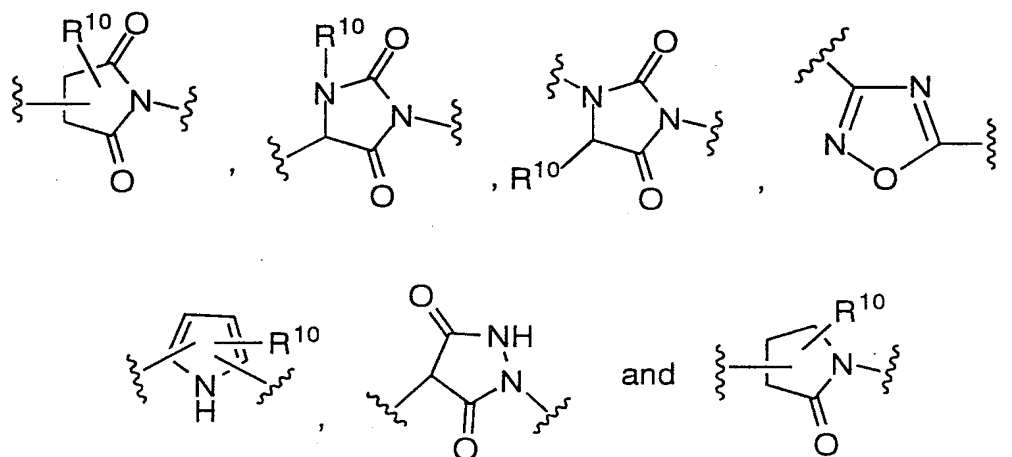
- 20            $(CH_2)_m$ ,  $(CH_2)_m-S-(CH_2)_n$ , and  $(CH_2)_m-NR^4-(CH_2)_n$ ,

wherein any methylene ( $CH_2$ ) carbon atom in Y, other than in  $R^4$ , can be substituted by one or two  $R^3$  substituents.

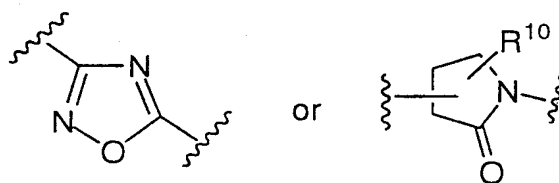
- In the compounds of the present invention, Z is preferably  
 25       selected from the group consisting of



More preferably Z is selected from the group consisting of



Most preferably Z is



In the compounds of the present invention, R<sup>1</sup> and R<sup>2</sup> are preferably selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-10 alkyl, C<sub>3</sub>-8 cycloalkyl, C<sub>3</sub>-8 cycloheteroalkyl, hydroxy, nitro, cyano, trifluoromethyl, and trifluoromethoxy.

5                    More preferably, R<sup>1</sup> and R<sup>2</sup> are selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-10 alkyl, C<sub>3</sub>-8 cycloalkyl, trifluoromethyl, and trifluoromethoxy.

10                    In the compounds of the present invention, R<sup>3</sup> is preferably selected from the group consisting of  
                      hydrogen,  
                      fluoro,  
                      trifluoromethyl,  
                      aryl,  
15                    C<sub>1</sub>-8 alkyl,  
                      arylC<sub>1</sub>-6 alkyl  
                      hydroxyl,  
                      oxo,  
                      arylaminocarbonyl,  
20                    aryl C<sub>1</sub>-5 alkylaminocarbonyl,  
                      aminocarbonyl, and  
                      aminocarbonyl C<sub>1</sub>-6 alkyl.

25                    More preferably, R<sup>3</sup> is selected from the group consisting of  
                      fluoro,  
                      aryl,  
                      C<sub>1</sub>-8 alkyl,  
                      arylC<sub>1</sub>-6 alkyl  
                      hydroxyl,  
30                    oxo, and  
                      arylaminocarbonyl.

In the compounds of the present invention, R<sup>4</sup> is preferably selected from the group consisting of

hydrogen,  
aryl,  
C<sub>3-8</sub> cycloalkyl,  
C<sub>1-8</sub> alkyl,  
5 C<sub>1-8</sub> alkylcarbonyl,  
arylcarbonyl,  
C<sub>1-6</sub> alkylsulfonyl,  
arylsulfonyl,  
arylC<sub>1-6</sub>alkylsulfonyl,  
10 arylC<sub>1-6</sub>alkylcarbonyl,  
C<sub>1-8</sub>alkylaminocarbonyl,  
arylC<sub>1-5</sub>alkylaminocarbonyl,  
arylC<sub>1-8</sub>alkoxycarbonyl, and  
C<sub>1-8</sub>alkoxycarbonyl.

15 More preferably, R<sup>4</sup> is selected from the group consisting of  
hydrogen,  
C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonyl,  
arylcarbonyl,  
20 arylC<sub>1-6</sub>alkylcarbonyl,  
C<sub>1-6</sub> alkylsulfonyl,  
arylsulfonyl, and  
arylC<sub>1-6</sub>alkylsulfonyl.

In one embodiment of the present invention, R<sup>5</sup> and R<sup>6</sup> are  
25 each independently selected from the group consisting of  
hydrogen,  
aryl,  
C<sub>1-8</sub> alkyl,  
aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
30 aryl C<sub>1-6</sub> alkyl,  
CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-, and  
HC≡C-(CH<sub>2</sub>)<sub>t</sub>-.

In a class of this embodiment of the present invention, R<sup>6</sup> is  
hydrogen and R<sup>5</sup> is selected from the group consisting of  
35 hydrogen,

aryl,  
 C<sub>1-8</sub> alkyl,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl C<sub>1-6</sub> alkyl,  
 5 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-, and  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-.

In a subclass of this class of the present invention, R<sup>6</sup>, R<sup>7</sup>, and R<sup>8</sup> are each hydrogen and R<sup>5</sup> is selected from the group consisting of

10 hydrogen,  
 aryl,  
 C<sub>1-8</sub> alkyl,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl C<sub>1-6</sub> alkyl,  
 15 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-, and  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-.

In another embodiment of the present invention, R<sup>7</sup> and R<sup>8</sup> are each independently selected from the group consisting of

20 hydrogen,  
 aryl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 arylcarbonylamino,  
 C<sub>1-8</sub> alkylsulfonylamino,  
 25 arylsulfonylamino,  
 C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
 arylsulfonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylsulfonylamino,  
 aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
 30 C<sub>1-8</sub> alkoxy carbonylamino,  
 C<sub>1-8</sub> alkoxy carbonylamino C<sub>1-8</sub> alkyl,  
 aryloxy carbonylamino C<sub>1-8</sub> alkyl,  
 aryl C<sub>1-8</sub> alkoxy carbonylamino,  
 aryl C<sub>1-8</sub> alkoxy carbonylamino C<sub>1-8</sub> alkyl,  
 35 C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,

arylcarbonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylcarbonylamino,  
 aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
 aminocarbonylamino C<sub>1-6</sub> alkyl,  
 5 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
 10 aminosulfonylamino C<sub>1-6</sub> alkyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
 15 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylthiocarbonylamino,  
 C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino, and  
 20 aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl.

In a class of this embodiment of the present invention, R<sup>8</sup> is  
 hydrogen and R<sup>7</sup> is selected from the group consisting of consisting of  
 hydrogen,  
 25 aryl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 aryl C<sub>1-6</sub> alkylcarbonylamino,  
 arylcarbonylamino,  
 C<sub>1-8</sub> alkylsulfonylamino,  
 30 aryl C<sub>1-6</sub> alkylsulfonylamino,  
 arylsulfonylamino,  
 C<sub>1-8</sub> alkoxycarbonylamino,  
 aryl C<sub>1-8</sub> alkoxycarbonylamino,  
 arylaminocarbonylamino,



(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino, and  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino.

5

In a subclass of this class of the present invention, R<sup>5</sup>, R<sup>6</sup>, and R<sup>8</sup> are each hydrogen and R<sup>7</sup> is selected from the group consisting of

hydrogen,  
 10 aryl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 aryl C<sub>1-6</sub> alkylcarbonylamino,  
 arylcarbonylamino,  
 C<sub>1-8</sub> alkylsulfonylamino,  
 15 aryl C<sub>1-6</sub> alkylsulfonylamino,  
 arylsulfonylamino,  
 C<sub>1-8</sub> alkoxycarbonylamino,  
 aryl C<sub>1-8</sub> alkoxycarbonylamino,  
 arylaminocarbonylamino,  
 20 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino, and  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino.

25 In the compounds of the present invention, R<sup>9</sup> is preferably selected from the group consisting of hydrogen, methyl, and ethyl.

More preferably, R<sup>9</sup> is hydrogen.

In the compounds of the present invention, R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> are preferably each independently selected from the group consisting of hydrogen and C<sub>1-8</sub> alkyl. More preferably R<sup>10</sup>, R<sup>11</sup>, and  
 30 R<sup>12</sup> are hydrogen.

In the compounds of the present invention, m is preferably an integer from 0 to 4, more preferably from 0 to 3.

In the compounds of the present invention, n is preferably an integer from 0 to 4, more preferably from 0 to 3.

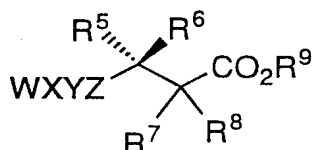
In the compounds of the present invention, r is preferably an integer from 1 to 2.

In the compounds of the present invention, s is preferably an integer from 0 to 2.

5 In the compounds of the present invention, t is preferably an integer from 0 to 2, more preferably from 0 to 1.

In the compounds of the present invention, v is preferably 0.

In certain embodiments of the present invention the compounds have the formula with the following designated  
10 stereochemistry:



wherein the substituents W, X, Y, Z, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup>, and the subscripts m, n, p, r, s, t, and v are as  
15 described above.

Illustrative but nonlimiting examples of compounds of the present invention that are useful as integrin receptor antagonists are the following:

20 Ethyl 3(S)-(3-fluorophenyl)-3-[2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthydin-2-yl)-propyl]-pyrrolidin-1-yl]-propionate;

Ethyl 3(S)-(3-fluorophenyl)-3-[2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthydin-2-yl)-propyl]-pyrrolidin-1-yl]-propionate;

25 Ethyl 3(S)-(2,3-dihydro-benzofuran-6-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionate;

Ethyl 3(S)-(2,3-dihydro-benzofuran-6-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionate;  
30

Ethyl 3(S)-(quinolin-3-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionate;

5 Ethyl 3(S)-(quinolin-3-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionate;

3(S)-(3-Fluorophenyl)-3-[2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl]-propionic acid;

10 3(S)-(3-Fluorophenyl)-3-[2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl]-propionic acid;

3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

15 3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

20 3(S)-(Quinolin-3-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3(S)-(Quinolin-3-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

25 2(S)-Benzenesulfonylamino-3-[3-(3-[1,8]naphthyridin-2-yl-propyl)-[1,2,4]oxadiazol-5-yl]-propionic acid;

3(S)-(6-Ethoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

30 3(S)-(6-Amino-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

- 3(S)-(4-Methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 5 3-(6-Methylamino-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(2-Fluoro-biphenyl-4-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 10 3(S)-(2-Oxo-2,3-dihydro-benzoxazol-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(4-Ethoxy-3-fluorophenyl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 15 3(S)-(5-Ethoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 20 3(S)-(5-Methoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(Ethynyl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 25 3(S)-(6-Methoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(2-Oxo-2,3-dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 30 3(S)-(2,3-Dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 35

- 3(S)-(2-Oxo-3,4-dihydro-2H-1-oxa-4,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 5 3(S)-(3,4-Dihydro-2H-1-oxa-4,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 10 3-(Furo-[2,3-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3-(2,3-Dihydrofuro[2,3-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 15 3-(Furo-[3,2-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3-(2,3-Dihydrofuro[3,2-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 20 3(S)-(Benzimidazol-2-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 25 3(S)-(1H-Imidazo[4,5-c]pyridin-2-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(Benzoxazol-2-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 30 3(S)-(1-Methyl-1H-pyrazol-4-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-pent-4-enoic acid;
- 35

and the pharmaceutically acceptable salts thereof.

Further illustrative of the present invention are compounds  
5 selected from the group consisting of

3(S)-(3-Fluorophenyl)-3-[2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl]-propionic acid;

10 3(S)-(3-Fluorophenyl)-3-[2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl]-propionic acid;

3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

15 3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3(S)-(Quinolin-3-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-  
20 2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3(S)-(Quinolin-3-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-  
2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

25 and the pharmaceutically acceptable salts thereof.

For use in medicine, the salts of the compounds of this  
invention refer to non-toxic "pharmaceutically acceptable salts." Other  
salts may, however, be useful in the preparation of the compounds  
30 according to the invention or of their pharmaceutically acceptable salts.  
Salts encompassed within the term "pharmaceutically acceptable salts"  
refer to non-toxic salts of the compounds of this invention which are  
generally prepared by reacting the free base with a suitable organic or  
inorganic acid. Representative salts include the following: acetate,  
35 benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate,

bromide, calcium, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts.

The compounds of the present invention can have chiral centers and occur as racemates, racemic mixtures, diastereomeric mixtures, and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the separate enantiomers or diastereomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985,

which is incorporated by reference herein in its entirety. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

5 The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

10 The term "integrin receptor antagonist," as used herein, refers to a compound which binds to and antagonizes either the  $\alpha v \beta 3$  receptor, the  $\alpha v \beta 5$  receptor, or the  $\alpha v \beta 6$  receptor, or a compound which binds to and antagonizes combinations of these receptors (for example, a dual  $\alpha v \beta 3 / \alpha v \beta 5$  receptor antagonist).

The term "bone resorption," as used herein, refers to the process by which osteoclasts degrade bone.

15 The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.).

20 The term "alkenyl" shall mean straight or branched chain alkenes of two to ten total carbon atoms, or any number within this range.

The term "alkynyl" shall mean straight or branched chain alkynes of two to ten total carbon atoms, or any number within this range.

25 The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

30 The term "cycloheteroalkyl," as used herein, shall mean a 3- to 8-membered fully saturated heterocyclic ring containing one or two heteroatoms chosen from N, O or S. Examples of cycloheteroalkyl groups include, but are not limited to piperidinyl, pyrrolidinyl, azetidiny, morpholinyl, piperazinyl.

The term "alkoxy," as used herein, refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g.,



C<sub>1-5</sub> alkoxy), or any number within this range (i.e., methoxy, ethoxy, etc.).

The term "aryl," as used herein, refers to a monocyclic or polycyclic system comprising at least one aromatic ring, wherein the  
 5 monocyclic or polycyclic system contains 0, 1, 2, 3, or 4 heteroatoms chosen from N, O, or S, and wherein the monocyclic or polycyclic system is either unsubstituted or substituted with one or more groups independently selected from hydrogen, halogen, C<sub>1-10</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl, aryl C<sub>1-8</sub> alkyl, amino, amino C<sub>1-8</sub> alkyl, C<sub>1-3</sub>  
 10 acylamino, C<sub>1-3</sub> acylamino C<sub>1-8</sub> alkyl, C<sub>1-6</sub> alkylamino, C<sub>1-6</sub> alkylamino C<sub>1-8</sub> alkyl, C<sub>1-6</sub> dialkylamino, C<sub>1-6</sub> dialkylamino-C<sub>1-8</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkoxy C<sub>1-6</sub> alkyl, hydroxycarbonyl, hydroxycarbonyl C<sub>1-6</sub> alkyl, C<sub>1-5</sub> alkoxycarbonyl, C<sub>1-3</sub> alkoxycarbonyl C<sub>1-6</sub> alkyl, hydroxycarbonyl C<sub>1-6</sub> alkyloxy, hydroxy, hydroxy C<sub>1-6</sub> alkyl, cyano, trifluoromethyl, oxo or C<sub>1-5</sub>  
 15 alkylcarbonyloxy. Examples of aryl include, but are not limited to, phenyl, naphthyl, pyridyl, pyrrol, pyrazolyl, pyrazinyl, pyrimidinyl, imidazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, indolyl, thienyl, furyl, dihydrobenzofuryl, benzo(1,3) dioxolane, oxazolyl, isoxazolyl and thiazolyl, which are either unsubstituted or substituted with one or more  
 20 groups independently selected from hydrogen, halogen, C<sub>1-10</sub> alkyl, C<sub>3-8</sub> cycloalkyl, aryl, aryl C<sub>1-8</sub> alkyl, amino, amino C<sub>1-8</sub> alkyl, C<sub>1-3</sub> acylamino, C<sub>1-3</sub> acylamino C<sub>1-8</sub> alkyl, C<sub>1-6</sub> alkylamino, C<sub>1-6</sub> alkylamino-C<sub>1-8</sub> alkyl, C<sub>1-6</sub> dialkylamino, C<sub>1-6</sub> dialkylamino C<sub>1-8</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkoxy C<sub>1-6</sub> alkyl, hydroxycarbonyl, hydroxycarbonyl  
 25 C<sub>1-6</sub> alkyl, C<sub>1-5</sub> alkoxycarbonyl, C<sub>1-3</sub> alkoxycarbonyl C<sub>1-6</sub> alkyl, hydroxycarbonyl C<sub>1-6</sub> alkyloxy, hydroxy, hydroxy C<sub>1-6</sub> alkyl, cyano, trifluoromethyl, oxo or C<sub>1-5</sub> alkylcarbonyloxy. Preferably, the aryl group is unsubstituted, mono-, di-, tri- or tetra-substituted with one to four of the above-named substituents; more preferably, the aryl group is  
 30 unsubstituted, mono-, di- or tri-substituted with one to three of the above-named substituents; most preferably, the aryl group is unsubstituted, mono- or di-substituted with one to two of the above-named substituents.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aryl C<sub>0-8</sub> alkyl) it shall be

interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C<sub>1-10</sub>) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl  
5 appears as its prefix root.

The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. Examples of arylalkyl include, but are not limited to, benzyl, fluorobenzyl, chlorobenzyl, phenylethyl,  
10 phenylpropyl, fluorophenylethyl, chlorophenylethyl, thienylmethyl, thienylethyl, and thienylpropyl. Examples of alkylaryl include, but are not limited to, toluene, ethylbenzene, propylbenzene, methylpyridine, ethylpyridine, propylpyridine and butylpyridine.

In the compounds of the present invention, two R<sup>1</sup>  
15 substituents, when on the same carbon atom, can be taken together with the carbon to which they are attached to form a carbonyl group.

In the compounds of the present invention, two R<sup>3</sup>  
substituents, when on the same carbon atom, can be taken together with the carbon atom to which they are attached to form a carbonyl group. In  
20 such instances, the limitation, that in the resultant compound the carbon atom or atoms to which R<sup>3</sup> is attached is itself attached to no more than one heteroatom, does not apply. Also, in the compounds of the present invention, two R<sup>3</sup> substituents, when on the same carbon atom, can be taken together with the carbon atom to which they are  
25 attached to form a cyclopropyl group.

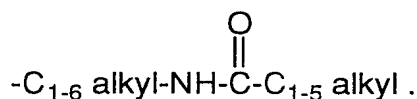
In the compounds of the present invention, R<sup>5</sup> and R<sup>6</sup> can be taken together with the carbon atom to which they are attached to form a carbonyl group. In such instances, the limitation, that in the resultant compound the carbon atom to which R<sup>5</sup> and R<sup>6</sup> is attached is  
30 itself attached to no more than one heteroatom, does not apply.

The term "halogen" shall include iodine, bromine, chlorine, and fluorine.

The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom. The term "oxo" means "=O". The term  
35 "carbonyl" means "C=O."

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or  
5 claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described  
10 first, followed by the adjacent functionality toward the point of attachment. For example, a C<sub>1-5</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl substituent is equivalent to



In choosing compounds of the present invention, one of  
15 ordinary skill in the art will recognize that the various substituents, i.e. W, X, Y, Z, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup>, and the subscripts m, n, p, r, s, t and v are to be chosen in conformity with well-known principles of chemical structure connectivity.

Representative compounds of the present invention typically  
20 display submicromolar affinity for the integrin receptors, particularly the  $\alpha v \beta 3$ ,  $\alpha v \beta 5$ , and/or  $\alpha v \beta 6$  receptors. Compounds of this invention are therefore useful for treating mammals suffering from a bone condition caused or mediated by increased bone resorption, who are in need of such therapy. Pharmacologically effective amounts of the compounds,  
25 including pharmaceutically acceptable salts thereof, are administered to the mammal, to inhibit the activity of mammalian osteoclasts.

The compounds of the present invention are administered in dosages effective to antagonize the  $\alpha v \beta 3$  receptor where such treatment is needed, as, for example, in the prevention or treatment of  
30 osteoporosis.

Further exemplifying the invention is the method wherein the integrin receptor antagonizing effect is an  $\alpha v \beta 3$  antagonizing effect.

An illustration of the invention is the method wherein the  $\alpha v \beta 3$  antagonizing effect is selected from inhibition of bone resorption, restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, viral disease, tumor growth, or metastasis. Preferably,  
5 the  $\alpha v \beta 3$  antagonizing effect is the inhibition of bone resorption.

An example of the invention is the method wherein the integrin receptor antagonizing effect is an  $\alpha v \beta 5$  antagonizing effect. More specifically, the  $\alpha v \beta 5$  antagonizing effect is selected from inhibition of: restenosis, angiogenesis, diabetic retinopathy, macular  
10 degeneration, inflammation, tumor growth, or metastasis.

Illustrating the invention is the method wherein the integrin receptor antagonizing effect is a dual  $\alpha v \beta 3 / \alpha v \beta 5$  antagonizing effect. More particularly, the dual  $\alpha v \beta 3 / \alpha v \beta 5$  antagonizing effect is selected from inhibition of bone resorption, restenosis, angiogenesis,  
15 diabetic retinopathy, macular degeneration, inflammation, viral disease, tumor growth, or metastasis.

Illustrating the invention is the method wherein the integrin receptor antagonizing effect is an  $\alpha v \beta 6$  antagonizing effect. More particularly, the  $\alpha v \beta 6$  antagonizing effect is selected from  
20 inhibition of angiogenesis, inflammatory response, or wound healing.

Illustrating the invention is the method wherein the  $\alpha v \beta 3$  antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of angiogenesis, inhibition of diabetic retinopathy, inhibition of macular degeneration, inhibition of  
25 atherosclerosis, inflammation, viral disease, or inhibition of tumor growth or metastasis. Preferably, the  $\alpha v \beta 3$  antagonizing effect is the inhibition of bone resorption.

More particularly illustrating the invention is a pharmaceutical composition comprising any of the compounds  
30 described above and a pharmaceutically acceptable carrier. Another example of the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition

comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

Further illustrating the invention is a method of treating and/or preventing a condition mediated by antagonism of an integrin receptor in a mammal in need thereof, comprising administering to the  
5 mammal a therapeutically effective amount of any of the compounds described above. Preferably, the condition is selected from bone resorption, osteoporosis, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, viral  
10 disease, cancer, tumor growth, and metastasis. More preferably, the condition is selected from osteoporosis and cancer. Most preferably, the condition is osteoporosis.

More specifically exemplifying the invention is a method of eliciting an integrin antagonizing effect in a mammal in need thereof,  
15 comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. Preferably, the integrin antagonizing effect is an  $\alpha v\beta 3$  antagonizing effect; more specifically, the  $\alpha v\beta 3$  antagonizing effect is selected from inhibition of bone resorption,  
20 inhibition of restenosis, inhibition of atherosclerosis, inhibition of angiogenesis, inhibition of diabetic retinopathy, inhibition of macular degeneration, inhibition of inflammation, inhibition of viral disease, or inhibition of tumor growth or metastasis. Most preferably, the  $\alpha v\beta 3$  antagonizing effect is inhibition of bone resorption. Alternatively, the  
25 integrin antagonizing effect is an  $\alpha v\beta 5$  antagonizing effect, an  $\alpha v\beta 6$  antagonizing effect, or a mixed  $\alpha v\beta 3$ ,  $\alpha v\beta 5$ , and  $\alpha v\beta 6$  antagonizing effect. Examples of  $\alpha v\beta 5$  antagonizing effects are inhibition of restenosis, atherosclerosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, viral disease, or tumor growth. Examples  
30 of dual  $\alpha v\beta 6$  antagonizing effects are inhibition of angiogenesis, inflammatory response and wound healing.

Additional examples of the invention are methods of inhibiting bone resorption and of treating and/or preventing osteoporosis in a mammal in need thereof, comprising administering to the

mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

Additional illustrations of the invention are methods of treating hypercalcemia of malignancy, osteopenia due to bone  
5 metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia, and glucocorticoid treatment in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical  
10 compositions described above.

More particularly exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment and/or prevention of osteoporosis in a mammal in need thereof. Still further exemplifying the invention is the  
15 use of any of the compounds described above in the preparation of a medicament for the treatment and/or prevention of bone resorption, tumor growth, cancer, restenosis, atherosclerosis, diabetic retinopathy, macular degeneration, inflammation, viral disease, and/or angiogenesis.

Also exemplifying the invention are compositions further comprising an active ingredient selected from the group consisting of  
20 a.) an organic bisphosphonate or a pharmaceutically acceptable salt or ester thereof,  
b.) an estrogen receptor modulator,  
25 c.) a cytotoxic/antiproliferative agent,  
d.) a matrix metalloproteinase inhibitor,  
e.) an inhibitor of epidermal-derived, fibroblast-derived, or platelet-derived growth factors,  
f.) an inhibitor of VEGF,  
30 g.) an inhibitor of Flk-1/KDR, Flt-1, Tck/Tie-2, or Tie-1,  
h.) a cathepsin K inhibitor, and  
i.) a prenylation inhibitor, such as a farnesyl transferase inhibitor or a geranylgeranyl transferase inhibitor or a dual farnesyl/geranylgeranyl transferase inhibitor;  
35 and mixtures thereof.

(See, B. Millauer et al., "Dominant-Negative Inhibition of Flk-1 Suppresses the Growth of Many Tumor Types in *Vivo*", Cancer Research, 56, 1615-1620 (1996), which is incorporated by reference herein in its entirety).

5 Preferably, the active ingredient is selected from the group consisting of:

- a.) an organic bisphosphonate or a pharmaceutically acceptable salt or ester thereof,
- b.) an estrogen receptor modulator, and
- 10 c.) a cathepsin K inhibitor; and mixtures thereof.

Nonlimiting examples of such bisphosphonates include alendronate, etidronate, pamidronate, risedronate, ibandronate, and pharmaceutically acceptable salts and esters thereof. A particularly preferred bisphosphonate is alendronate, especially alendronate  
15 monosodium trihydrate.

Nonlimiting examples of estrogen receptor modulators include estrogen, progesterin, estradiol, droloxifene, raloxifene, and tamoxifene.

Nonlimiting examples of cytotoxic/antiproliferative agents  
20 are taxol, vincristine, vinblastine, and doxorubicin.

Cathepsin K, formerly known as cathepsin O2, is a cysteine protease and is described in PCT International Application Publication No. WO 96/13523, published May 9, 1996; U.S. Patent No. 5,501,969, issued March 3, 1996; and U.S. Patent No. 5,736,357, issued April 7, 1998,  
25 all of which are incorporated by reference herein in their entirety.

Cysteine proteases, specifically cathepsins, are linked to a number of disease conditions, such as tumor metastasis, inflammation, arthritis, and bone remodeling. At acidic pH's, cathepsins can degrade type-I collagen. Cathepsin protease inhibitors can inhibit osteoclastic bone  
30 resorption by inhibiting the degradation of collagen fibers and are thus useful in the treatment of bone resorption diseases, such as osteoporosis.

The present invention is also directed to combinations of the compounds of the present invention with one or more agents useful in the prevention or treatment of osteoporosis. For example, the  
35 compounds of the instant invention may be effectively administered in

combination with effective amounts of other agents such as an organic bisphosphonate, an estrogen receptor modulator, or a cathepsin K inhibitor.

Additional illustrations of the invention are methods of  
5 treating tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound described above and one or more agents known to be cytotoxic/antiproliferative. Also, the compounds of the present invention can be administered in combination with radiation therapy for treating  
10 tumor growth and metastasis.

In addition, the integrin  $\alpha v \beta 3$  antagonist compounds of the present invention may be effectively administered in combination with a growth hormone secretagogue in the therapeutic or prophylactic treatment of disorders in calcium or phosphate metabolism and  
15 associated diseases. These diseases include conditions which can benefit from a reduction in bone resorption. A reduction in bone resorption should improve the balance between resorption and formation, reduce bone loss or result in bone augmentation. A reduction in bone resorption can alleviate the pain associated with osteolytic  
20 lesions and reduce the incidence and/or growth of those lesions. These diseases include: osteoporosis (including estrogen deficiency, immobilization, glucocorticoid induced and senile), osteodystrophy, Paget's disease, myositis ossificans, Bechterew's disease, malignant hypercalcemia, metastatic bone disease, periodontal disease,  
25 cholelithiasis, nephrolithiasis, urolithiasis, urinary calculus, hardening of the arteries (sclerosis), arthritis, bursitis, neuritis and tetany. Increased bone resorption can be accompanied by pathologically high calcium and phosphate concentrations in the plasma, which would be alleviated by this treatment. Similarly, the present invention would be  
30 useful in increasing bone mass in patients with growth hormone deficiency. Thus, preferred combinations are simultaneous or alternating treatments of an  $\alpha v \beta 3$  receptor antagonist of the present invention and a growth hormone secretagogue, optionally including a third component comprising an organic bisphosphonate, preferably  
35 alendronate monosodium trihydrate.



In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant  
5 invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment, and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating integrin-mediated conditions includes in principle  
10 any combination with any pharmaceutical composition useful for treating osteoporosis.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or  
15 indirectly, from combination of the specified ingredients in the specified amounts.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills,  
20 powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, topical (e.g., ocular eyedrop), subcutaneous, intramuscular or transdermal (e.g., patch) form, all using forms well known to those of ordinary skill in the pharmaceutical  
25 arts. An effective but non-toxic amount of the compound desired can be employed as an  $\alpha v \beta 3$  antagonist.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the  
30 severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the  
35 condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral  
5 administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active  
10 ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously; compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be  
15 administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be  
20 administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are  
25 typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

30 For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like;  
35 for oral administration in liquid form, the oral drug components can be

combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable  
5 binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium  
10 benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small  
15 unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the  
20 compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted  
25 with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters,  
30 polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

In the schemes and examples below, various reagent symbols and abbreviations have the following meanings:

AcOH:	Acetic acid.
35 BH <sub>3</sub> •DMS:	Borane•dimethylsulfide.

	BOC(Boc):	t-Butyloxycarbonyl.
	BOP:	Benzotriazol-1-yloxytris(dimethylamino)- phosphonium hexafluorophosphate.
	CBZ(Cbz):	Carbobenzyloxy or benzyloxycarbonyl.
5	CDI:	Carbonyldiimidazole.
	CH <sub>2</sub> Cl <sub>2</sub> :	Methylene chloride.
	CH <sub>3</sub> CN:	Acetonitrile
	CHCl <sub>3</sub> :	Chloroform.
	DEAD:	Diethyl azodicarboxylate.
10	DIAD:	Diisopropyl azodicarboxylate.
	DIBAH or	
	DIBAL-H:	Diisobutylaluminum hydride.
	DIPEA:	Diisopropylethylamine.
	DMAP:	4-Dimethylaminopyridine.
15	DME:	1,2-Dimethoxyethane.
	DMF:	Dimethylformamide.
	DMSO:	Dimethylsulfoxide.
	DPFN:	3,5-Dimethyl-1-pyrazolylformamidinium nitrate.
	EDC:	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide • HCl
20	EtOAc:	Ethyl acetate.
	EtOH:	Ethanol.
	HOAc:	Acetic acid.
	HOAT:	1-Hydroxy-7-azabenzotriazole
	HOBT:	1-Hydroxybenzotriazole.
25	IBCF:	Isobutylchloroformate
	LDA:	Lithium diisopropylamide.
	MeOH:	Methanol.
	MMNG	1,1-methyl-3-nitro-1-nitrosoguanidine
	NEt <sub>3</sub> :	Triethylamine.
30	NMM:	N-methylmorpholine.
	PCA•HCl:	Pyrazole carboxamidinium hydrochloride.
	Pd/C:	Palladium on activated carbon catalyst.
	Ph:	Phenyl.
	pTSA	p-Toluenesulfonic acid.
35	TEA:	Triethylamine.

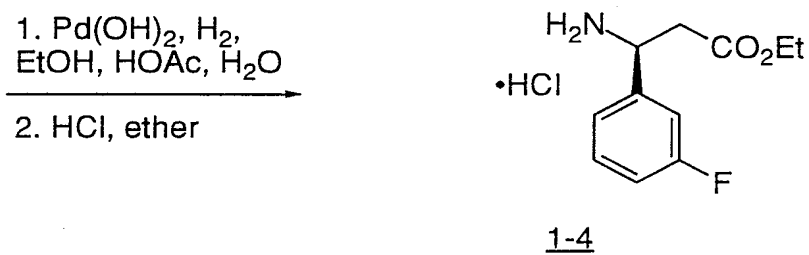
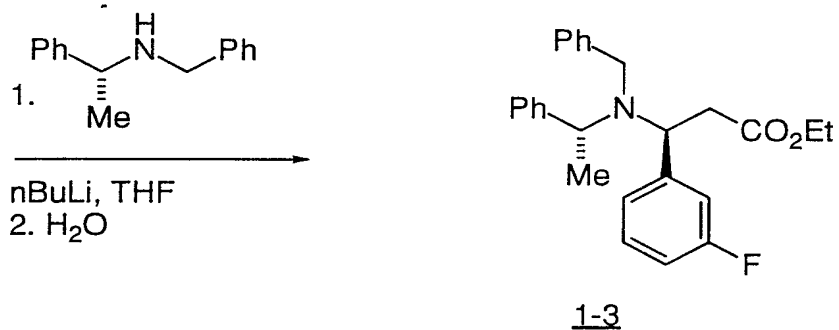
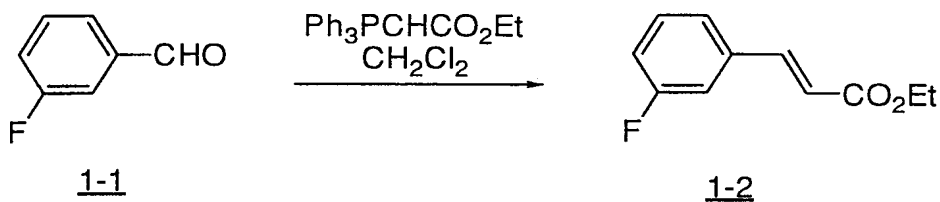
- TFA: Trifluoroacetic acid.  
THF: Tetrahydrofuran.  
TLC: Thin Layer Chromatography.  
TMEDA: N,N,N',N'-Tetramethylethylenediamine.  
5 TMS: Trimethylsilyl.

The novel compounds of the present invention can be prepared according to the procedure of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The compounds illustrated in the  
10 examples are not, however, to be construed as forming the only genus that is considered as the invention. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative  
15 procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

The following Schemes and Examples describe procedures for making representative compounds of the present invention. Moreover, by utilizing the procedures described in detail in PCT  
20 International Application Publication Nos. WO95/32710, published 7 December 1995, and WO95/17397, published 29 June 1995, both of which are incorporated by reference herein in their entirety, in conjunction with the disclosure contained herein, one of ordinary skill in the art can readily prepare additional compounds of the present invention claimed  
25 herein. Additionally, for a general review describing the synthesis of  $\beta$ -alanines which can be utilized as the C-terminus of the compounds of the present invention, see Cole, D.C., *Recent Stereoselective Synthetic Approaches to  $\beta$ -Amino Acids*, *Tetrahedron*, 1994, 50, 9517-9582; Juaristi, E, *et al.*, *Enantioselective Synthesis of  $\beta$ -Amino Acids*, *Aldrichimica Acta*, 1994, 27, 3. In particular, synthesis of the 3-methyl- $\beta$ -alanine is  
30 taught in Duggan, M.F. *et al.*, *J. Med. Chem.*, 1995, 38, 3332-3341; the 3-ethynyl- $\beta$ -alanine is taught in Zablocki, J.A., *et al.*, *J. Med. Chem.*, 1995, 38, 2378-2394; the 3-(pyridin-3-yl)- $\beta$ -alanine is taught in Rico, J.G. *et al.*, *J. Org. Chem.*, 1993, 58, 7948-7951; and the 2-amino- and 2-tosylamino- $\beta$ -  
35 alanines are taught in Xue, C-B, *et al.*, *Biorg. Med. Chem. Letts.*, 1996,

6, 339-344. The references described in this paragraph are all also incorporated by reference herein in their entirety.

SCHEME 1



Ethyl 3-fluorocinnamate (1-2)

To a solution of 3-fluorobenzaldehyde 1-1 (18.16 g, 146 mmol) in dichloromethane (500 mL) was added ethyl (triphenylphosphoranylidene)acetate (61.2 g; 176 mmol), and the  
5 resulting solution was stirred at room temperature for 18 hr. After evaporation of the solvent, the residue was swirled with ether/hexane and filtered. The filtrate was concentrated and then purified on a plug of silica gel eluting with hexane/EtOAc 9:1. Removal of the solvent  
10 afforded the title compound 1-2 as an oil (~95% trans) which was used without further purification in the next step.  
<sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 1.36 (3H, t), 4.28 (2H, q), 6.43 (1H, d), 7.08 (1H, m), 7.2-7.4 (3H, m), 7.64 (1H, d).

N-Benzyl-(R)-α-methylbenzyl-3(S)-fluorophenyl-β-alanine ethyl ester (1-3)

15 To a solution of N-benzyl-(R)-α-methylbenzylamine (33.4 g, 158 mmol) in THF (450 mL) at 0°C was added n-butyllithium (1.6M in hexanes; 99 mL, 158 mmol). The dark violet solution was stirred at 0°C for 30 minutes, cooled to -78°C, and the ester 1-2 (29.2 g, 150 mmol) in THF (100 mL) was added over 5 minutes. The resulting solution was  
20 stirred at -78°C for 1 hr., then warmed to room temperature. After 2 hrs, the mixture was poured into water and extracted with EtOAc, washed with water then brine, dried and concentrated *in vacuo* to give an oil. Column chromatography (silica gel; hexane/EtOAc 1:1 then pure EtOAc) gave the title compound 1-3.  
25 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.06 (3H, t), 1.28 (3H, d), 2.52 (1H, dd), 2.62 (1H, dd), 3.66 (1H, d), 3.72 (1H, d), 3.95 (2H, q), 4.44 (1H, dd), 6.95 (1H, m), 7.1-7.5 (13H, m).

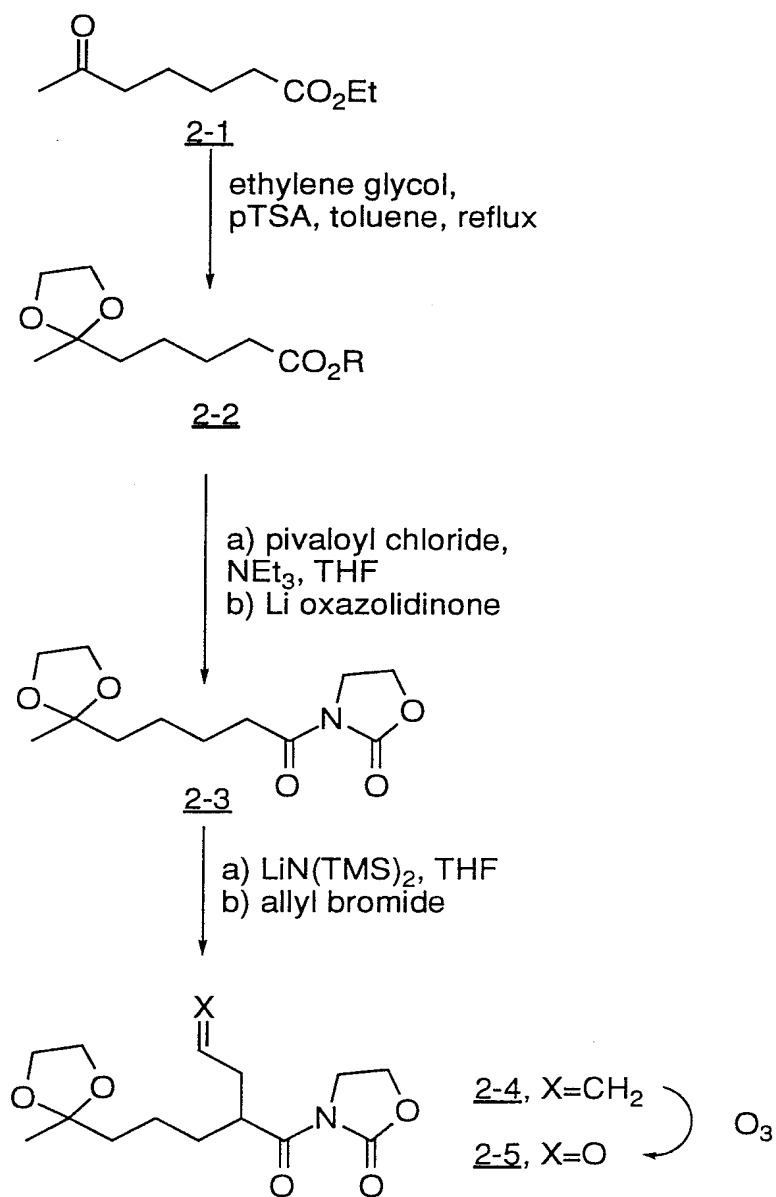
3(S)-Fluorophenyl-β-alanine ethyl ester hydrochloride (1-4)

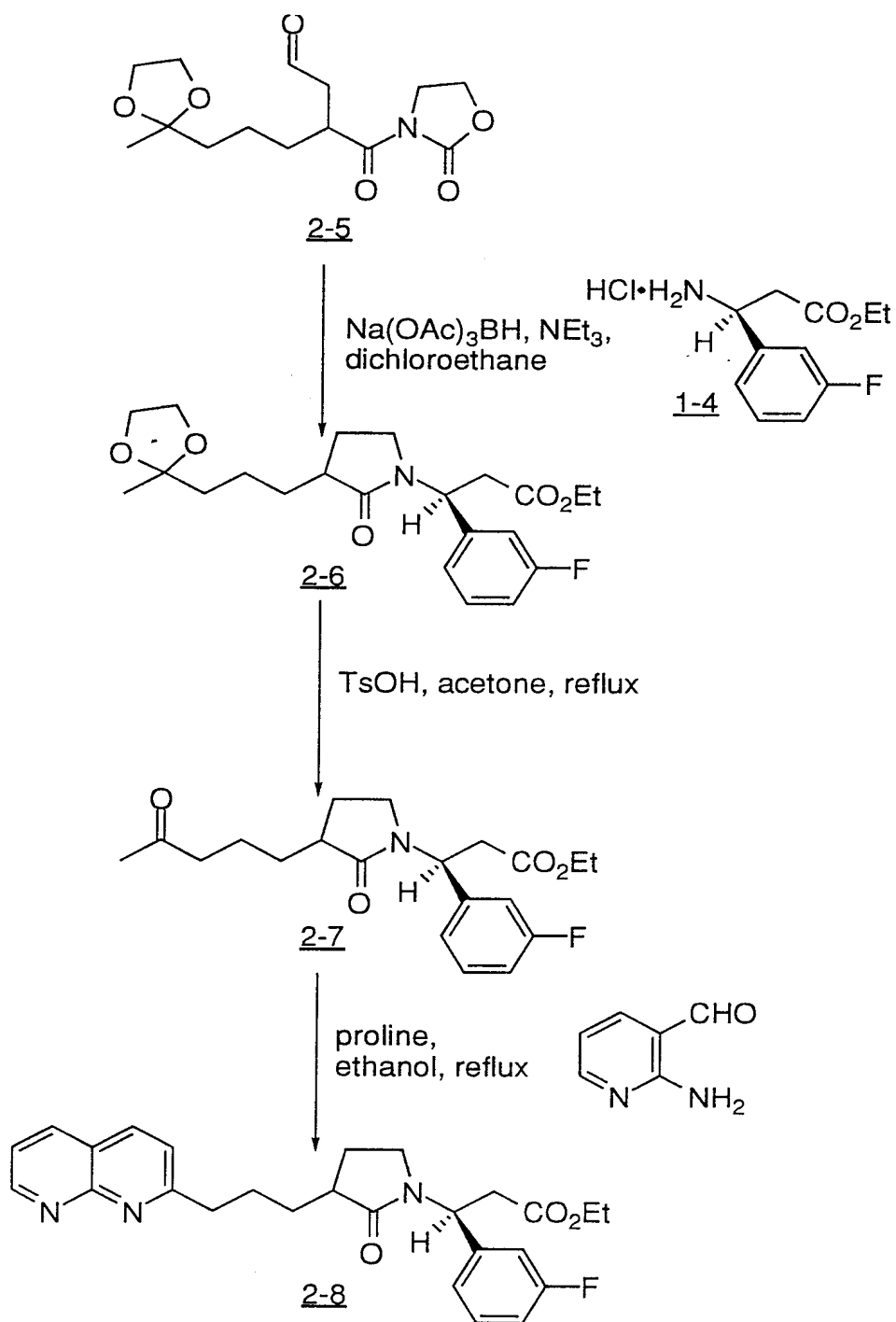
30 A solution of the N-benzyl-(R)-α-methylbenzylamine 1-3 (28.2 g, 69.6 mmol) in ethanol (300 mL), acetic acid (30 mL) and water (3 mL) was degassed with argon for 30 minutes. Pd(OH)<sub>2</sub> on carbon (20% dry weight; 2.6 g) was added and the mixture then stirred under a hydrogen atmosphere (balloon) for 2 hours. The mixture was filtered  
35 through celite and the solvent removed *in vacuo* to give an oil. This oil

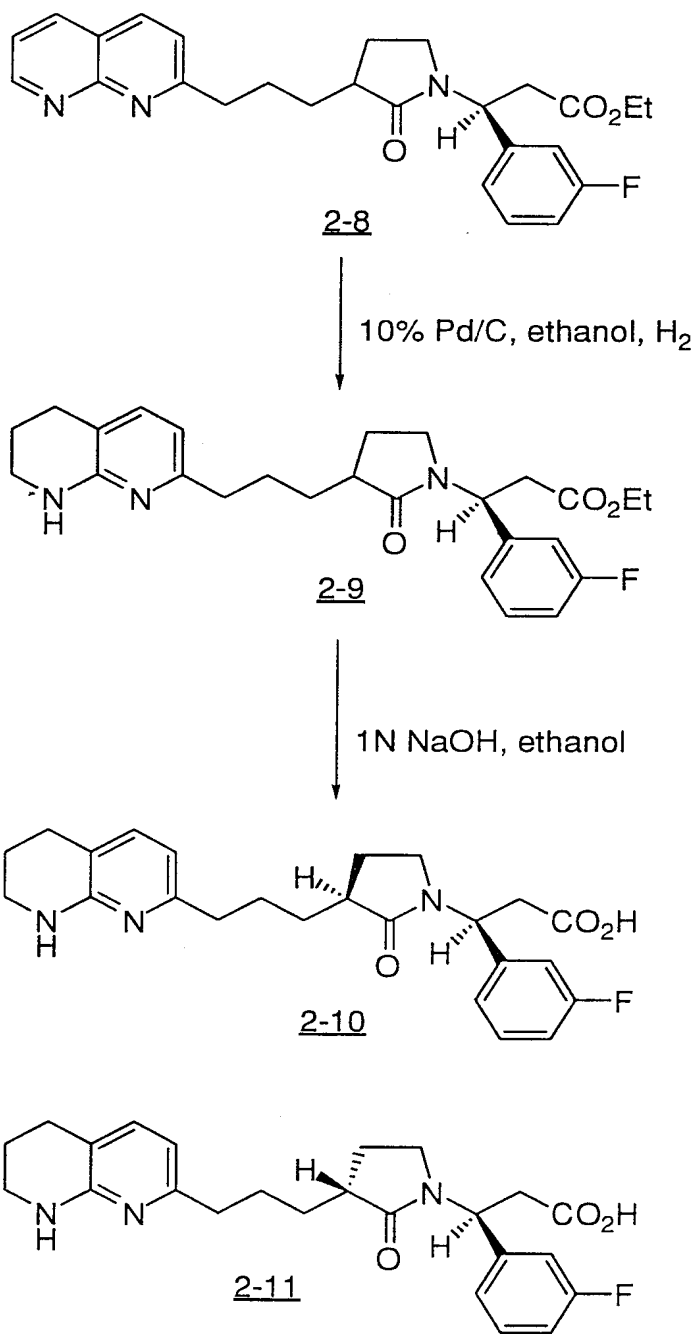
was dissolved in 200 mL ether and to this solution was added 60 mL 1N HCl in ether to yield a precipitate. Filtration and washing the solid with ether/hexane then gave the title compound 1-4 as a white solid.

<sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 1.21 (3H, t), 3.0-3.2 (2H, m), 4.16 (2H, q), 4.76 (1H, t),  
5 7.2-7.35 (3H, m), 7.5 (1H, m).



SCHEME 2

SCHEME 2 (CONTINUED)

SCHEME 2 (CONTINUED)

5-(2-methyl-[1,3]dioxolan-2-yl)-pentanoic acid (2-2)

A mixture of ketone 2-1 (18 g, 105 mmol), ethylene glycol (3.2 ml, 110 mmol), p-TSA (50 mg, 0.2713 mmol) and toluene (300 mL) was heated to reflux with azeotropic removal of water for 24 hours. The reaction mixture was diluted with EtOAc and then washed with sat. NaHCO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>), and concentrated. The residue was dissolved in EtOH (200 ml) and then treated with 1N NaOH (120 ml, 120 mmol). After 2 h, the reaction was poured into 600 mL 2:1 Et<sub>2</sub>O/10% KHSO<sub>4</sub>. The organic portion was separated, washed with brine, dried (MgSO<sub>4</sub>) and concentrated to give acid 2-2 as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.93 (m, 4H), 2.36 (m, 2H), 1.63 (m, 4H), 1.46 (m, 2H), 1.31 (s, 3H).

3-[5-(2-methyl-[1,3]dioxolan-2-yl)-pentanoyl]-oxazolidin-2-one (2-3)

To a stirred solution of 2-2 (16.0 g, 85.5 mmol), NEt<sub>3</sub> (13.1 ml, 94.1 mmol) and THF (400 mL) at -78°C was added pivaloyl chloride (11.6 ml, 94.1 mmol). The mixture was warmed to 0°C for 1.0 h and then recooled to -78°C. To a stirred solution of 2-oxazolidinone (9.3g, 106.9 mmol) and THF (200 ml) at -78°C was added nBuLi (43.0 ml, 106.9 mmol, 2.5M in hexanes) dropwise over 10 minutes. After 20 minutes, the lithium reagent was transferred to the mixed anhydride via cannula. After 10 minutes, the reaction was warmed to 0°C for 1.0h. The mixture was diluted with ethyl acetate, washed with sat. NaHCO<sub>3</sub>, brine, and dried over MgSO<sub>4</sub>. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 40% - 50% EtOAc/hexanes) to give 2-3 as a colorless foam. TLC R<sub>f</sub> = 0.19 (silica, 40% EtOAc/hexanes) <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.41 (t, J=8.1 Hz, 2H), 4.02 (t, J=8.1 Hz, 2H), 3.93 (m, 4H), 3.93 (t, J=7.3 Hz, 2H), 1.66 (m, 4H), 1.48 (m, 2H), 1.31 (s, 3H).

3-(2-[3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-pent-4-enoyl)-oxazolidin-2-one (2-4)

To a stirred solution of 2-3 (6.0 g, 23.3 mmol) and THF (125 mL) at -78°C was added LiN(TMS)<sub>2</sub> (18.9 mL, 37.8 mmol, 1.0 M in THF)

dropwise over 10 minutes. After 20 minutes, allyl bromide was added. After 10 minutes, the reaction was warmed to 0°C. After 4.0 h, the reaction was diluted with EtOAc, washed with sat. NaHCO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (silica, 50%

5 EtOAc/ hexanes) gave 2-4 as a yellow oil.

TLC R<sub>f</sub> = 0.26 (silica, 50% EtOAc/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.76 (m, 1H), 5.02 (m, 1H), 4.40 (t, J=8.3 Hz, 2H), 4.02 (m, 2H), 3.99 (m, 4H), 2.39 (m, 1H), 2.27 (m, 1H), 1.72 (m, 1H), 1.62 (m, 2H) 1.39 - 1.53 (m, 3H), 1.30 (s, 3H).

10

6-(2-methyl-[1,3]dioxolan-2-yl)-3-(2-oxo-oxazolidine-3-carbonyl)-hexanal (2-5)

To a stirred solution of 2-4 (4.0 g, 13.5 mmol), sudan III (10 mg) and CH<sub>2</sub>Cl<sub>2</sub> (350 mL) at -78°C under argon was bubbled ozone until

15 red solution changed to yellow-orange. The solution was purged with argon for 30 minutes. PPh<sub>3</sub> (5.28g, 20.3 mmol) was added followed by the removal of the cooling bath. After 3.0 h, the reaction was concentrated. Flash chromatography (silica, 20% - 50% EtOAc/ hexanes) gave 2-5 as a yellow oil.

20 TLC R<sub>f</sub> = 0.15 (silica, 50% EtOAc/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.74 (s, 1H), 4.43 (m, 2H), 4.15 (m, 1H), 4.03 (m, 2H), 3.91 (m, 4H), 3.04 (m, 1H), 2.67 (dd, J=3.9 Hz, 18.6 Hz, 1H), 1.65 (m, 3H), 1.45 (m, 3H), 1.29 (s, 3H).

25 3(S)-(3-Fluorophenyl)-3-(3-[3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-2-oxo-pyrrolidin-1-yl)-propionic acid ethyl ester (2-6)

A mixture of 2-5 (302 mg, 1.11 mmol), 1-4 (300 mg, 1.21 mmol), Na(OAc)<sub>3</sub>BH (321 mg, 1.52 mmol) and NEt<sub>3</sub> (0.28 mL, 2.02 mmol) in DCE (10 mL) was stirred for 48 h. The mixture was diluted with ethyl acetate, washed with sat. NaHCO<sub>3</sub>, brine, and dried over MgSO<sub>4</sub>.

30

Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 50:35:14:1 hexanes/ chloroform/ ethyl acetate/ MeOH) to give 2-6 as a white solid.

TLC R<sub>f</sub> = 0.41 (silica, 70:25:5 chloroform/ ethyl acetate/ MeOH)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.30 (m, 1H), 7.07 (m, 1H), 6.98 (m 3H), 5.68 (m, 1H), 4.12 (m, 2H), 3.92 (m, 4H), 3.30 (m, 1H), 2.97 (m, 3H), 2.38 (m, 1H), 2.14 (m, 1H), 1.86 (m, 1H), 1.64 (m, 4H), 1.42 (m, 2H), 1.30 (2s, 3H), 1.22 (t, J=7.3Hz, 3H).

5

3(S)-(3-Fluorophenyl)-3-[2-oxo-3-(4-oxo-pentyl)-pyrrolidin-1-yl]-  
propionic acid ethyl ester (2-7)

A solution of 2-6 (450 mg, 1.10 mmol), p-TSA (50 mg) and acetone (50 mL) was heated at reflux for 4 hr. The cooled reaction mixture was diluted with EtOAc and then washed with sat. NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>), and concentrated to afford 2-7 as a yellow solid.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.30 (m, 1H), 7.06 (m, 1H), 6.98 (m, 2H), 5.67 (m, 1H), 4.12 (m, 2H), 3.23 (m, 1H), 2.97 (m, 2H), 2.33 - 2.49 (m, 3H), 2.14 (2s, 3H), 1.54 - 1.86 (m, 5H), 1.33 (m, 1H), 1.22 (t, J=7.1Hz, 3H).

15

3(S)-(3-Fluorophenyl)-3-[3-(3-[1,8]naphthyridin-2-yl-propyl)-2-oxo-pyrrolidin-1-yl]-propionic acid ethyl ester (2-8)

A mixture of 2-7 (430 mg, 1.18 mmol), 2-amino-3-formylpyridine (144 mg, 1.18 mmol; for prep., see *JOC* 1983,48, 3401) and proline (136 mg, 1.18 mmol) in absolute ethanol (20 mL) was heated at reflux for 12 h. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 50% ethyl acetate/ chloroform - 70:25:5 chloroform/ethyl acetate/MeOH) to give 2-8 as a yellow solid.

TLC R<sub>f</sub> = 0.30 (70:25:5 chloroform/ethyl acetate/MeOH).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.08 (m, 1H), 8.16 (dd, J=2.0 Hz, 8.0 Hz 1H), 8.11 (d, J=8.3 Hz, 1H), 7.42 (m, 2H), 7.27 (m, 1H), 7.06 (m, 1H), 6.97 (m, 2H), 5.66 (m, 1H), 4.11 (m, 2H), 3.29 (m, 1H), 2.95 - 3.07 (m, 5H), 2.46 (m, 1H), 2.18 (m, 1H), 1.98 (m, 2H), 1.71 (m, 2H), 1.46 (m, 1H), 1.19 (m, 3H).

30

3(S)-(3-Fluorophenyl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid ethyl ester (2-9)

A mixture of 2-8 (340 mg, 0.7991 mmol) and 10% Pd/carbon (170 mg) in EtOH (10 mL) was stirred under a balloon of hydrogen for 4

h. Following filtration and evaporative removal of the solvent, the residue was chromatographed (silica gel, 70:25:5 chloroform/ethyl acetate/MeOH) to give 2-9 as a yellow oil.

TLC Rf = 0.16 (70:25:5 chloroform/ethyl acetate/MeOH).

- 5  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 (m, 1H), 6.98 (m, 4H), 6.33 (m, 1H), 5.66 (m, 1H), 4.76 (b s, 1H), 4.10 (m, 2H), 3.38 (m, 1H), 3.28 (m, 1H), 2.95 (m, 3H), 2.68 (t,  $J=6.3$  Hz, 2H), 2.55 (m, 2H), 2.40 (m, 1H), 2.13 (m, 1H) 1.92 (m, 4H), 1.61 (m, 3H), 1.37 (m, 1H), 1.23 (m, 3H).

- 10 3(S)-(3-Fluorophenyl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid (2-10 and 2-11)

To a solution of 2-9 (300 mg, 0.6614 mmol) in EtOH (3 mL) was added 1N NaOH (0.725 ml, 0.725 mmol). After stirring for 1 h, the solvents were evaporated and the residue was chromatographed (silica gel, 25:10:1:1 - 15:10:1:1 ethyl acetate/EtOH/water/ $\text{NH}_4\text{OH}$ ) to give 2-10 and 2-11 as pure diastereomeric white solids.

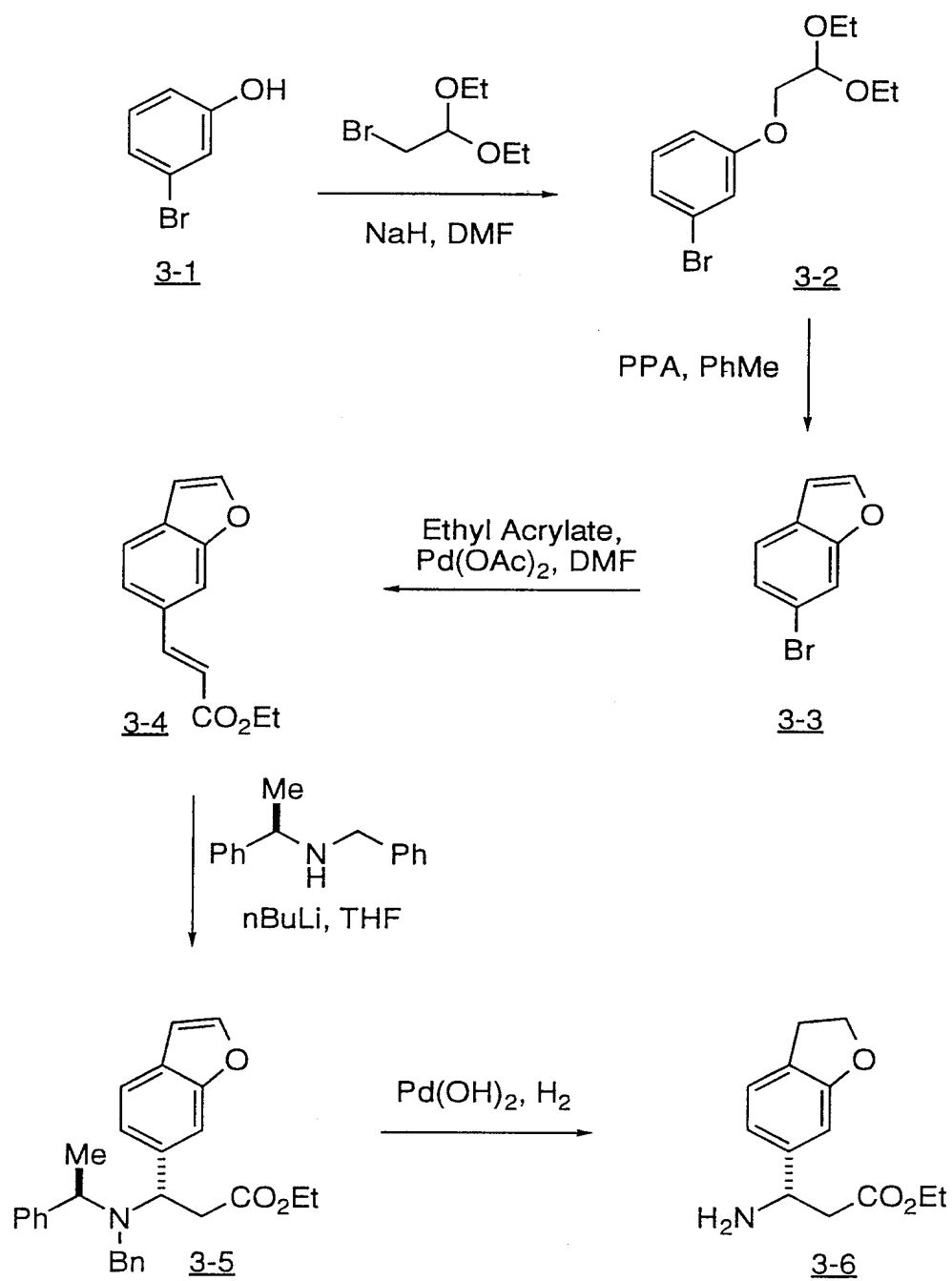
TLC Rf = 0.31 (2-10) (15:10:1:1 ethyl acetate/EtOH/water/ $\text{NH}_4\text{OH}$ ).

TLC Rf = 0.24 (2-11) (15:10:1:1 ethyl acetate/EtOH/water/ $\text{NH}_4\text{OH}$ ).

- 20  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ , 2-10)  $\delta$  7.44 (d,  $J=7.3$  Hz, 1H), 7.37 (m, 1H), 7.14 (m, 1H), 7.06 (m, 2H), 6.50 (d,  $J=7.3$  Hz, 1H), 5.78 (m, 1H), 3.55 (m, 1H), 3.46 (m, 2H), 3.11 (m, 1H), 2.61 -2.97 (m, 7H), 2.12 (m, 1H) 1.74 -1.95 (m, 7H).

- 25  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ , 2-11)  $\delta$  7.34 (m, 2H), 7.15 (m, 2H), 7.03 (m, 1H), 6.47 (d,  $J=7.3$  Hz, 1H), 5.50 (m, 1H), 3.46 (m, 3H), 3.00 (m, 1H), 2.79 (m, 3H), 2.62 (m, 2H), 2.54 (m, 1H), 2.23 (m, 1H), 1.93 (m, 2H), 1.69 (m, 5H), 1.44 (m, 1H).

## SCHEME 3





1-Bromo-3-(2,2-diethoxy-ethoxy)-benzene (3-2)

To a suspension of NaH (2.77 g, 115.6 mmol) in DMF (100 mL) at 0°C was added a solution of 3-bromophenol 3-1 in DMF (40 mL) over 40 min. After the addition was complete, the solution was stirred  
5 for an additional 30 min. The solution was then treated with neat bromoacetaldehyde diethyl acetal (17.36 g, 115.6 mmol). The solution was heated at 100°C for 8 h, cooled to room temperature, and extracted with Et<sub>2</sub>O (3 x 200 mL). The combined organic extracts were washed with 10% aq. NaOH (100 mL) and brine (100 mL), dried over MgSO<sub>4</sub>,  
10 filtered and concentrated to give 3-2 as a yellow oil.  
TLC R<sub>f</sub> = 0.4 (10% ethyl acetate/hexanes).  
<sup>1</sup>H NMR (300 MHz, CHCl<sub>3</sub>) δ 7.19-7.05 (m, 3H), 6.85 (d, 1H), 4.81 (t, 1H, J=6.8 Hz), 3.99 (d, 2H, J=6.8 Hz), 3.71 (m, 4H), 1.22 (t, 6H, J=7.1 Hz)

6-Bromo-benzofuran (3-3)

To a solution of the acetal 3-2 in toluene (200 mL) was added polyphosphoric acid (20 g). The biphasic mixture was heated to 100°C and stirred at this temperature for 4 h. The mixture was cooled to room temperature, poured onto ice, and extracted with Et<sub>2</sub>O (2 x 200 mL). The  
20 combined organic extracts were washed with saturated aq. NaHCO<sub>3</sub> and brine. The solution was dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography (100% hexanes) to give the product 3-3 as a yellow oil.  
TLC R<sub>f</sub> = 0.3 (100% hexanes).  
25 <sup>1</sup>H NMR (300 MHz, CHCl<sub>3</sub>) δ 7.68 (s, 1H), 7.60 (d, 1H, J=2.1 Hz), 7.46 (d, 1H, J=8.4 Hz), 7.36 (dd, 1H, J=8.1, 1.5 Hz), 6.75 (dd, 1H, J=7.1, 0.9 Hz).

3-(Benzofuran-6-yl)-acrylic acid ethyl ester (3-4)

A mixture of the 6-bromobenzofuran 3-3 (1.74 g, 8.79 mmol),  
30 ethyl acrylate (1.09 g, 10.98 mmol), Pd(OAc)<sub>2</sub> (0.099 g, 0.44 mmol), tri-*o*-tolylphosphine (0.268 g, 0.880 mmol), and sodium acetate (3.60 g, 43.9 mmol) in DMF (10 mL) was heated to 100°C in a sealed tube for 4 h. The mixture was cooled to room temperature, diluted with water, and extracted with Et<sub>2</sub>O (2 x 40 mL). The combined organic extracts were  
35 washed with brine (30 mL), dried over MgSO<sub>4</sub>, filtered, and

concentrated. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to give the ester 3-4 as an off-white solid.

TLC Rf = 0.3 (10% ethyl acetate/hexanes).

<sup>1</sup>H NMR (300 MHz, CHCl<sub>3</sub>) δ 7.78 (d, 1H, J=15.9 Hz), 7.68 (d, 1H, J=2.4 Hz), 7.66 (s, 1H), 7.59 (d, 1H, J=8.4 Hz), 7.43 (dd, 1H, J=9.0, 1.5 Hz), 6.78 (m, 1H), 6.47 (d, 1H, J=15.9 Hz), 4.27 (q, 2H, J=7.2 Hz), 1.34 (t, 3H, J=7.2 Hz).

10 3(S)-(Benzofuran-6-yl)-3-[benzyl-(1(R)-phenyl-ethyl)-amino]-propionic acid ethyl ester (3-5)

A solution of N-benzyl-α-(R)-methylbenzylamine (1.32 g, 6.30 mmol) in THF (25 mL) at 0°C was treated with n-BuLi (2.52 mL of a 2.5 M soln in hexanes). The resulting solution was stirred at 0°C for 30 min and then cooled to -78°C. A solution of acrylate 3-4 (0.681 g, 3.15 mmol) in THF (5 mL) was added. After stirring for 15 min at -78°C, satd. aq. NH<sub>4</sub>Cl soln (5 mL) was added and the cold bath removed. The mixture was warmed to room temperature, and extracted with Et<sub>2</sub>O (2 x 40 mL). The combined organic extracts were washed with brine (30 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to give the β-aminoester 3-5 as a yellow oil.

TLC Rf = 0.8 (10% ethanol/dichloromethane).

<sup>1</sup>H NMR (300 MHz, CHCl<sub>3</sub>) δ 7.58 (m, 3H), 7.41 (m, 2H), 7.22 (m, 9H), 7.59 (s, 1H), 4.58 (m, 1H), 4.05 (m, 1H), 3.91 (q, 2H, J=7.1 Hz), 3.72 (m, 2H), 2.62 (m, 2H), 1.21 (d, 3H, J=7.2 Hz), 1.03 (t, 3H, J=7.1 Hz).

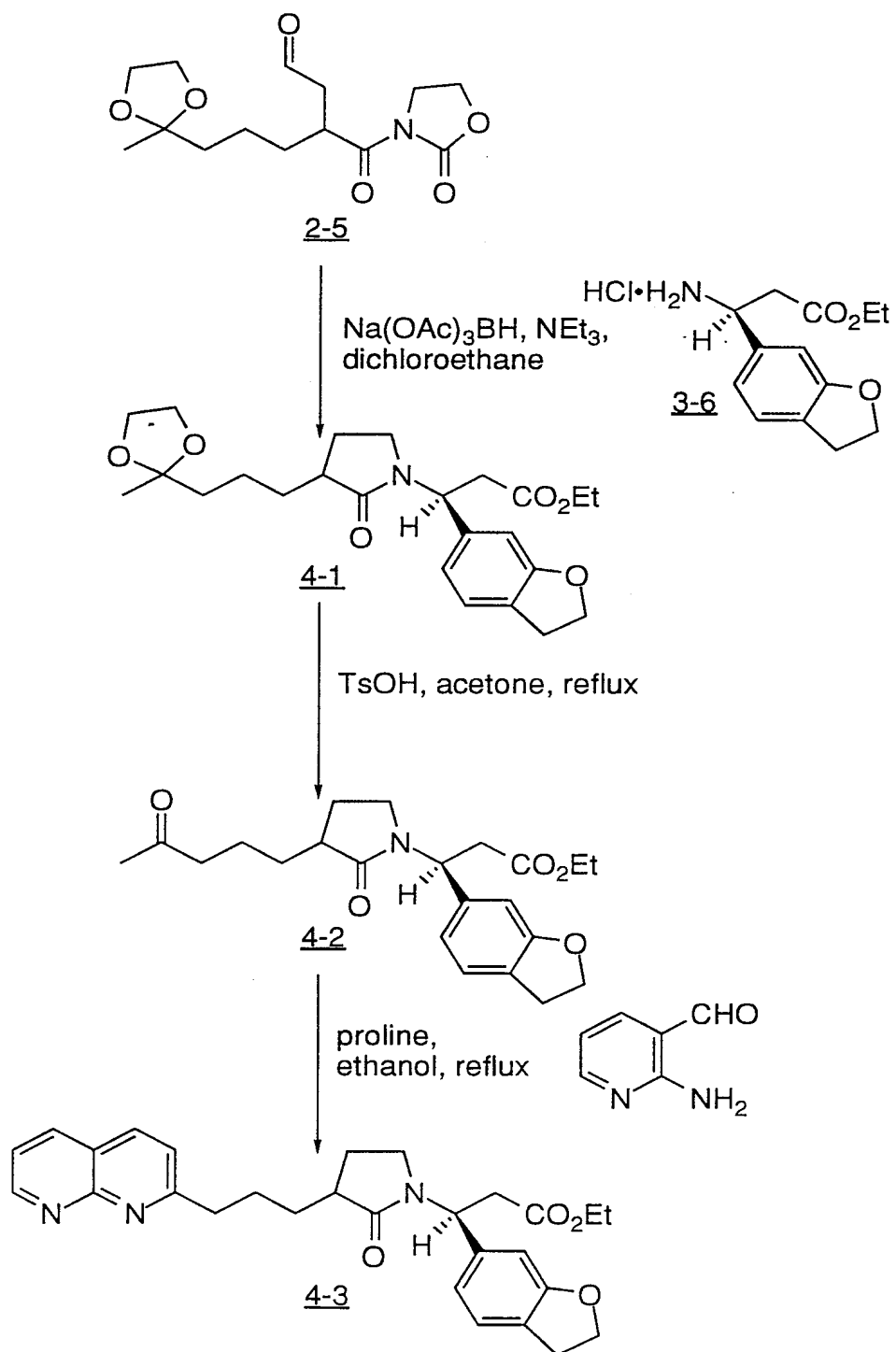
3(S)-Amino-3-(2,3-dihydro-benzofuran-6-yl)-propionic acid ethyl ester (3-6)

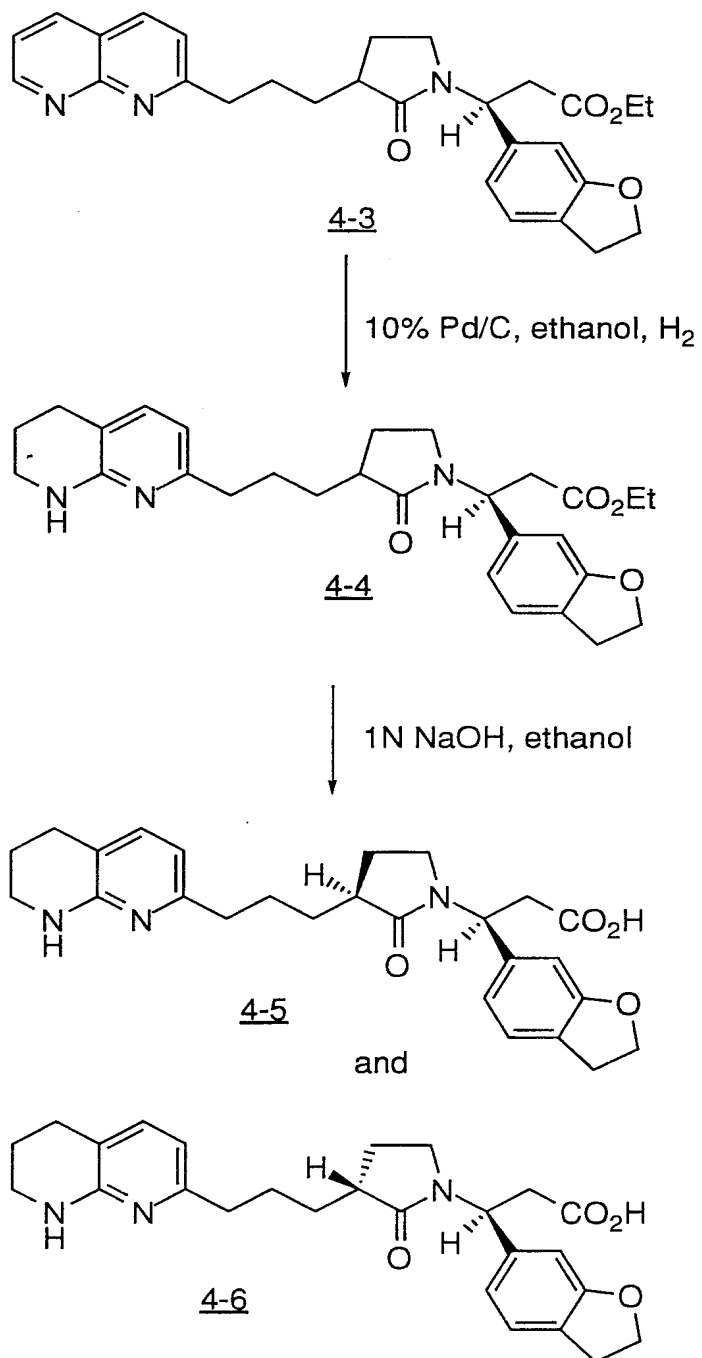
A mixture of the dibenzylamine 3-5 (1.19 g, 2.78 mmol) in EtOH/H<sub>2</sub>O/AcOH (26 mL/3 mL/1.0 mL) was degassed with argon and treated with Pd(OH)<sub>2</sub> (1.19 g). The mixture was placed under 1 atm of H<sub>2</sub>. After stirring for 18 h, the mixture was diluted with EtOAc, and filtered through celite. The filtrate was concentrated and the residue purified by flash chromatography (10% ethyl acetate/dichloromethane) to give the ester 3-6 as a white solid.

TLC Rf = 0.25 (10% ethanol/dichloromethane).

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ) as the trifluoroacetate salt:  $\delta$  7.25 (d, 1H,  $J=8.1$  Hz), 6.88 (m, 1H), 7.66 (s, 1H), 6.82 (s, 1H), 4.58 (m, 3H), 4.12 (m, 2H), 3.30 (m, 1H), 3.19 (m, 2H), 2.98 (m, 2H), 1.11 (t, 3H,  $J=7.2$  Hz).

5

SCHEME 4

SCHEME 4 (CONTINUED)

3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(3-[3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-2-oxo-pyrrolidin-1-yl)-propionic acid ethyl ester (4-1)

A mixture of 2-5 (440 mg, 1.6 mmol), 3-6 (400 mg, 1.5 mmol), Na(OAc)<sub>3</sub>BH (469 mg, 2.25 mmol) and NEt<sub>3</sub> (0.41 mL, 3.0 mmol) in  
5 dichloroethane (10 mL) was stirred for 48 h. The mixture was diluted with ethyl acetate, washed with sat. NaHCO<sub>3</sub>, brine, and dried over MgSO<sub>4</sub>. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 50:35:14:1 hexanes/ chloroform/ ethyl acetate/ MeOH) to give 4-1 as a white solid.  
10 TLC R<sub>f</sub> = 0.45 (silica, 70:25:5 chloroform/ ethyl acetate/ MeOH)  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.15 (m, 1H), 6.78 (m, 1H), 6.70 (m 1H), 5.63 (m, 1H), 4.58 (m, 2H), 4.12 (q, J=7 Hz, 2H), 3.92 (m, 4H), 3.40-2.80 (m, 6H), 2.38 (m, 1H), 2.14 (m, 1H), 1.86 (m, 1H), 1.64 (m, 4H), 1.42 (m, 2H), 1.30 (m, 3H), 1.22 (t, J=7 Hz, 3H).

15

3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-[2-oxo-3-(4-oxo-pentyl)-pyrrolidin-1-yl]-propionic acid ethyl ester (4-2)

A solution of 4-1 (600 mg, 1.4 mmol), p-TSA (20 mg) and acetone (50 mL) was heated at reflux for 4 hr. The cooled reaction  
20 mixture was diluted with EtOAc and then washed with sat. NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>), and concentrated to afford 4-2 as a colorless oil.  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.15 (m, 1H), 6.78 (m, 1H), 6.70 (m 1H), 5.63 (m, 1H), 4.58 (m, 2H), 4.12 (q, J=7 Hz, 2H), 3.35-2.90 (m, 6H), 2.49-2.30 (m,  
25 3H), 2.13 (2s, 3H), 1.90-1.50 (m, 5H), 1.33 (m, 1H), 1.22 (t, J=7 Hz, 3H).

3(S)- (2,3-Dihydro-benzofuran-6-yl)-3-[3-(3-[1,8]naphthyridin-2-yl-propyl)-2-oxo-pyrrolidin-1-yl]-propionic acid ethyl ester (4-3)

A mixture of 4-2 (540 mg, 1.4 mmol), 2-amino-3-formylpyridine (170 mg, 1.4 mmol; for prep. see JOC 1983,48, 3401) and proline (161 mg, 1.4 mmol) in absolute ethanol (20 mL) was heated at reflux for 12 h. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 50% ethyl acetate/ chloroform 70:25:5 chloroform/ethyl acetate/MeOH) to give 4-3 as a yellow oil.  
35 TLC R<sub>f</sub> = 0.21 (70:25:5 chloroform/ethyl acetate/MeOH).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.08 (m, 1H), 8.16 (dd, J=2.0 Hz, 8.0 Hz 1H), 8.11 (d, J=8.3 Hz, 1H), 7.42 (m, 2H), 7.10 (m, 1H), 6.78 (m, 1H), 6.70 (m, 1H), 5.63 (m, 1H), 4.57 (m, 2H), 4.11 (m 2H), 3.29 (m, 1H), 3.30-2.80 (m, 9H), 2.40 (m, 1H), 2.18 (m, 1H), 1.98 (m, 2H), 1.70-1.50 (m, 2H), 1.46 (m, 1H), 1.19 (m, 3H).

3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid ethyl ester (4-4)

10 A mixture of 4-3 (460 mg, 1.0 mmol) and 10% Pd/carbon (300 mg) in EtOH (20 mL) was stirred under a balloon of hydrogen for 3 h. Following filtration and evaporative removal of the solvent, the residue was chromatographed (silica gel, 70:25:5 chloroform/ethyl acetate/MeOH) to give 4-4 as a yellow oil.

15 TLC Rf = 0.15 (70:25:5 chloroform/ethyl acetate/MeOH).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.18 (m, 1H), 7.07 (m, 2H), 6.80 (m, 1H), 6.70 (m, 1H), 6.37 (m, 1H), 5.64 (m, 1H), 4.76 (bs, 1H), 4.55 (m, 2H), 4.10 (q, J=7 Hz, 2H), 3.40 (m, 1H), 3.28 (m, 2H), 3.28 (m, 1H), 3.19 (m, 2H), 3.00 (m, 1H), 2.95 (m, 2H), 2.69 (m 2H), 2.55 (m, 2H), 2.37 (m, 1H), 2.13 (m, 1H) 1.92 (m, 3H), 1.75-1.30 (m, 4H), 1.23 (m, 3H).

3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid (4-5 and 4-6)

25 To a solution of 4-4 (380 mg, 0.79 mmol) in EtOH (2 mL) was added 1N NaOH (0.93 ml, 0.93 mmol). After stirring for 1 h, the solvents were evaporated and the residue was chromatographed (silica gel, 25:10:1:1 - 15:10:1:1 ethyl acetate/EtOH/water/NH<sub>4</sub>OH) to give 4-5 and 4-6 as pure diastereomeric white solids.

30 TLC Rf = 0.37 (isomer A) (15:10:1:1 ethyl acetate/EtOH/water/NH<sub>4</sub>OH).

TLC Rf = 0.28 (isomer B) (15:10:1:1 ethyl acetate/EtOH/water/NH<sub>4</sub>OH).

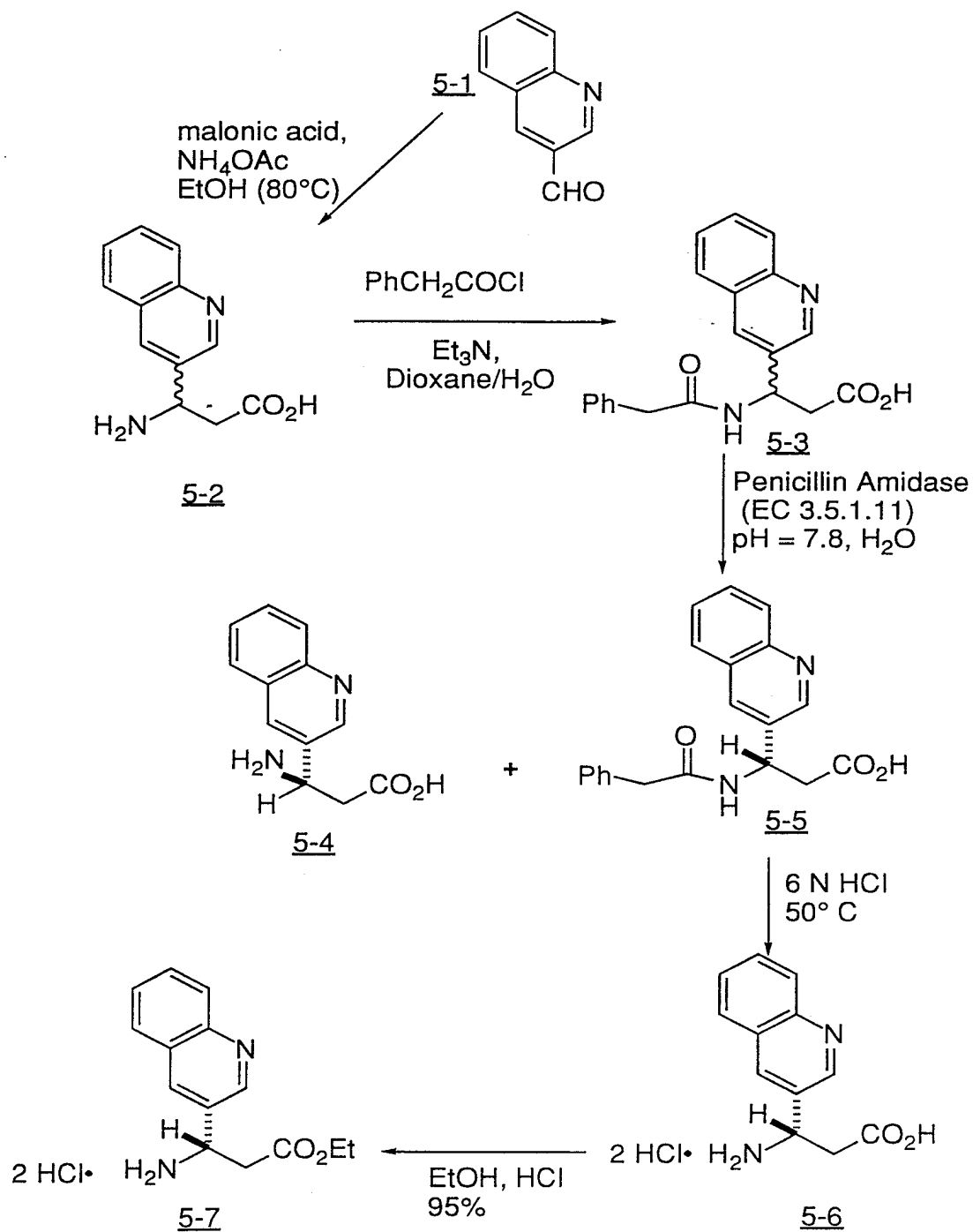
<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD, Isomer A) δ 7.44 (d, J=7 Hz, 1H), 7.16 (d, J=7 Hz, 1H), 6.80 (d, J=7 Hz, 1H), 6.70 (s, 1H), 6.48 (d, J=7 Hz, 1H), 5.46 (m, 1H), 4.50 (m, 2H), 3.60-2.50 (m, 13H), 1H), 2.15 -1.70 (m, 8H),

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ , Isomer B)  $\delta$  7.40 (d,  $J=7$  Hz, 1H), 7.13 (d,  $J=7$  Hz, 1H), 6.80 (d,  $J=7$  Hz, 1H), 6.68 (s, 1H), 6.50 (d,  $J=7$  Hz, 1H), 5.72 (m, 1H), 4.53 (m, 2H), 3.44 (m, 3H), 3.15 (m, 4H), 2.97 (m, 1H), 2.70-2.40 (m, 6H), 2.20 (m, 1H), 2.00-1.40 (m, 6H).

5



## SCHEME 5



3-Quinolin-3-yl-propionic acid (5-2).

A solution containing quinoline-3-carboxaldehyde 5-1 (5 g, 31.8 mmol), malonic acid (3.6 g, 35.0 mmol), and ammonium acetate (5.0 g, 63.6 mmol) in anhydrous ethanol (125 mL) was heated at reflux for 12 h. After cooling to room temperature, the resulting white solid was collected by filtration and washed with cold ethanol (150 mL) and then dried under vacuum to provide 5-2 as a white solid (3.84 g, 17.8 mmol, 56%).

<sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O): δ 8.91 (d, J = 2 Hz 1H), 8.21 (d, J = 2 Hz, 1H), 8.12 (d, J = 8 Hz, 1H), 7.84 (d, J = 7 Hz, 1H), 7.72 (t, J = 7 Hz, 1H), 7.54 (t, J = 7 Hz, 1H), 4.72 (m, 1H), 2.73 (m, 2H).

3-Phenylacetyl-amino-3-(quinolin-3-yl)-propionic (5-3)

A 0° solution of 5-2 (3.5 g, 16.2 mmol) and NaHCO<sub>3</sub> (2.7 g, 32.4 mmol) in 50% aqueous dioxane (100 mL) was treated dropwise with a solution of phenylacetyl chloride (3.00 g, 19.4 mmol) in 25 mL of dioxane. The resulting solution was stirred at 0° for 2.5h., then warmed to room temperature, diluted with H<sub>2</sub>O (50 mL) and washed with ether (2 x 100 mL). The aqueous layer was adjusted to pH = 3 with 3N HCl and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 150 mL). The pooled organic extracts were dried, filtered and concentrated to afford 5-3 as an off-white solid. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 8.85 (d, J = 2 Hz 1H), 8.20 (d, J = 2 Hz, 1H), 8.00 (d, J = 8 Hz, 1H), 7.86 (d, J = 7 Hz, 1H), 7.76 (t, J = 7 Hz, 1H), 7.52 (t, J = 7 Hz, 1H), 7.28 (m, 6H), 5.53 (t, J = 6.8 Hz, 1H), 3.57 (s, 2H), 2.96 (m, 2H).

3(S)-(Quinolin-3-yl)-propionic acid dihydrochloride (5-6)

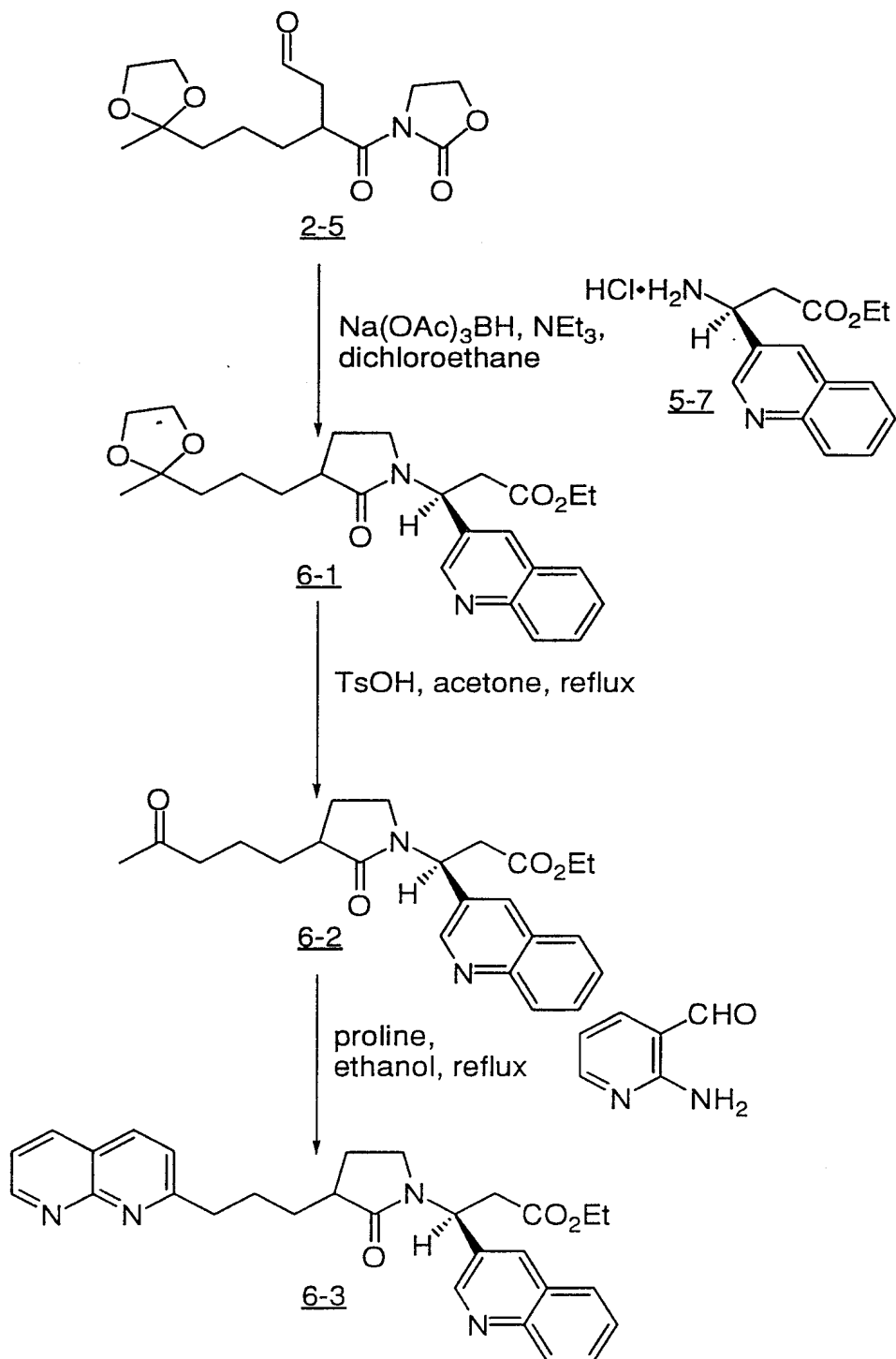
Acid 5-3 (5.0 g, 15 mmol) was suspended in water (3.5 L), then treated with 1N NaOH (15 mL) to afford a clear solution. Penicillin amidase (Sigma, EC 3.5.1.11, 10,000 U) in 0.1 M phosphate buffer was added. The pH of the mixture was adjusted to 7.8 with 1N NaOH and the solution was stirred at room temperature for 4 days. The reaction was monitored periodically by HPLC and the reaction stopped once the 50% conversion was reached. Next, the reaction solution was cooled to 0°C and adjusted to pH = 3 with 3N HCl. An oily yellow precipitate formed

which was collected by filtration, then washed with water to afford crude 5-5 (1.8 g, 5.3 mmol). The filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 500 mL) to afford additional 5-5 contaminated by phenylacetic acid. Both batches of crude 5-5 were combined and stirred in 6 N HCl (200 mL) at  
5 50° for 12 h then cooled, washed with ether (2 x 100 mL) and evaporated to afford 5-6.

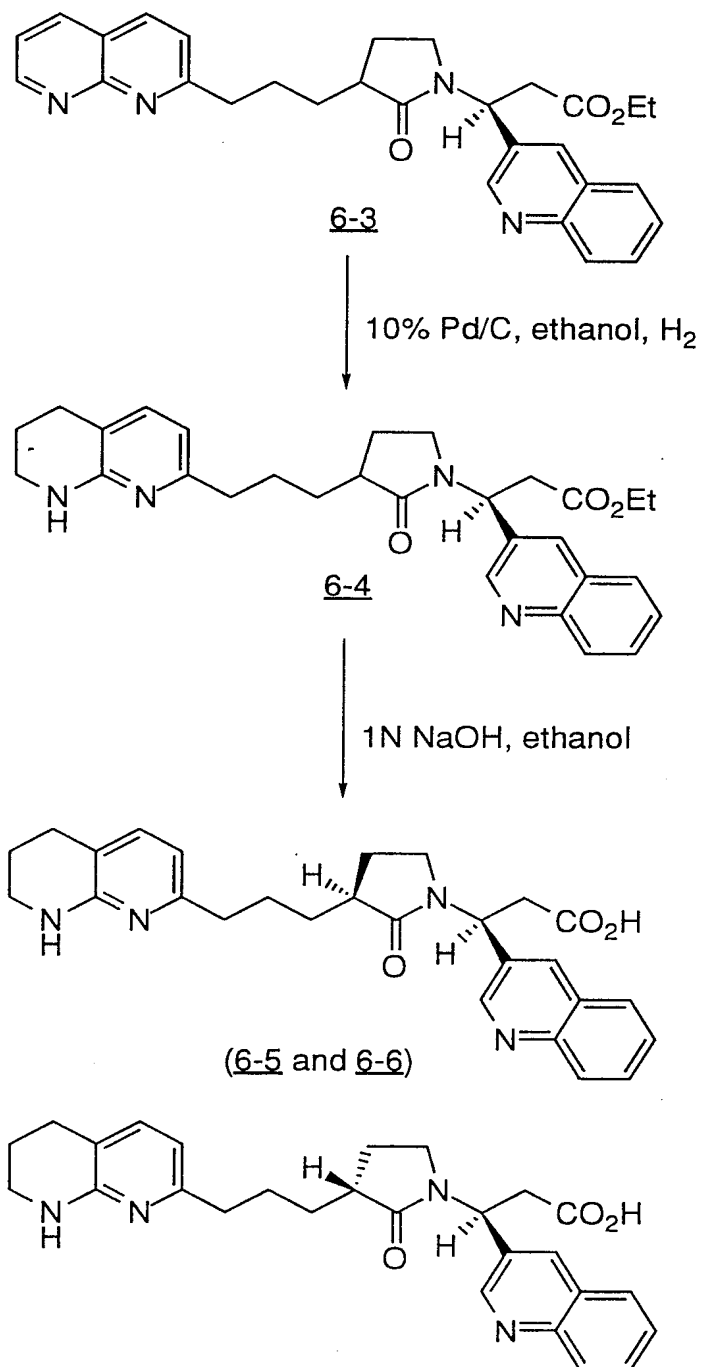
3(S)-(Quinolin-3-yl)-propionic acid ethyl ester dihydrochloride (5-7).

The resolved acid 5-6 was converted to 5-7 by refluxing in  
10 ethanolic HCl.  
<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 9.25 (d, J = 2 Hz 1H), 8.31 (d, J = 2 Hz, 1H),  
8.15 (d, J = 8 Hz, 1H), 7.84 (d, J = 7 Hz, 1H), 7.72 (t, J = 7 Hz, 1H), 7.54 (t, J  
= 7 Hz, 1H), 4.72 (m, 1H), 4.15 (q, J = 6 Hz, 2H), 2.73 (m, 2H) 1.18 (t, J = 6  
Hz, 3H).

15

SCHEME 6

SCHEME 6 (CONTINUED)



3(S)-(Quinolin-3-yl)-3-(3-[3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-2-oxo-pyrrolidin-1-yl)-propionic acid ethyl ester (6-1)

---

A mixture of 2-5 (377 mg, 1.3 mmol), 5-6 (400 mg, 1.3 mmol), Na(OAc)<sub>3</sub>BH (400 mg, 2.0 mmol) and NEt<sub>3</sub> (0.35 mL, 2.6 mmol) in  
5 dichloroethane (10 mL) was stirred for 24 h. The mixture was diluted with ethyl acetate, washed with sat. NaHCO<sub>3</sub>, brine, and dried over MgSO<sub>4</sub>. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 50:35:14:1 hexanes/ chloroform/ ethyl acetate/ MeOH) to give 6-1 as a yellow oil.  
10 TLC R<sub>f</sub> = 0.47 (silica, 70:25:5 chloroform/ ethyl acetate/ MeOH)  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.85 (m, 1H), 8.10-7.40 (m, 5H), 5.90 (m, 1H), 4.12 (q, J=7 Hz, 2H), 3.90 (m, 4H), 3.38 (m, 1H), 3.20-2.95 (m, 3H), 2.40 (m, 1H), 2.14 (m, 1H), 1.90 (m, 1H), 1.74-1.30 (m, 4H), 1.30 (ds, 3H), 1.22 (t, J=7 Hz, 3H).

15

3(S)-(Quinolin-3-yl)-3-[2-oxo-3-(4-oxo-pentyl)-pyrrolidin-1-yl]-propionic acid ethyl ester (6-2)

---

A solution of 6-1 (380 mg, 1.0 mmol), p-TSA (20 mg) and acetone (50 mL) was heated at reflux for 4 hr. The cooled reaction  
20 mixture was diluted with EtOAc and then washed with sat. NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>), and concentrated to afford 6-2 as a yellow oil.  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.74 (m, 1H), 8.05-7.40 (m, 5H), 5.90 (m, 1H), 4.13 (m, 2H), 3.38 (m, 1H), 3.20-2.95 (m, 3H), 2.50-2.10 (m, 4H), 2.13 (d, J=5 Hz, 3H), 1.90-1.20 (m, 6H), 1.22 (t, J=7 Hz, 3H).

25

3(S)-(Quinolin-3-yl)-3-[3-(3-[1,8]naphthyridin-2-yl-propyl)-2-oxo-pyrrolidin-1-yl]-propionic acid ethyl ester (6-3)

---

A mixture of 6-2 (396 mg, 1.0 mmol), 2-amino-3-formylpyridine (138 mg, 1.2 mmol; for prep. see *JOC* 1983,48, 3401) and  
30 proline (218 mg, 2.0 mmol) in absolute ethanol (15 mL) was heated at reflux for 12 h. Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 50% ethyl acetate/chloroform to 70:25:5 chloroform/ethyl acetate/MeOH) to give 6-3 as a yellow oil.  
TLC R<sub>f</sub> = 0.23 (70:25:5 chloroform/ethyl acetate/MeOH).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.08 (m, 1H), 8.85 (m, 1H), 8.20-7.50 (m, 9H), 5.90 (m, 1H), 4.11 (m, 2H), 3.40 (m, 1H), 3.20-2.90 (m, 6H), 2.60-1.40 (m, 6H), 1.22 (m, 3H).

5    3(S)-(Quinolin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid ethyl ester (6-4)

A mixture of 6-3 (380 mg, 0.8 mmol) and 10% Pd/carbon (200 mg) in EtOH (20 mL) was stirred under a balloon of hydrogen for 6 h. Following filtration and evaporative removal of the solvent, the residue  
10    was chromatographed (silica gel, 70:25:5 to 70:20:10 chloroform/ethyl acetate/MeOH) to give 6-4 as a yellow oil.

TLC R<sub>f</sub> = 0.20 (70:20:10 chloroform/ethyl acetate/MeOH).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.86 (m, 1H), 8.08 (m, 2H), 7.80 (m, 1H), 7.72 (m, 1H), 7.57 (m, 1H), 7.03 (m, 1H), 6.33 (m, 1H), 5.90 (m, 1H), 4.11 (m,  
15    2H), 3.40 (m, 3H), 3.15-2.00 (m, 9H), 2.00-1.30 (m, 8H), 1.22 (m, 3H).

3(S)-(Quinolin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid (6-5 and 6-6)

To a solution of 6-4 (300 mg, 0.62 mmol) in EtOH (3 mL) was  
20    added 1N NaOH (0.68 mL, 0.68 mmol). After stirring for 2 h, the solvents were evaporated and the residue was chromatographed (silica gel, 25:10:1:1 - 15:10:1:1 ethyl acetate/EtOH/water/NH<sub>4</sub>OH) to give 6-5 and 6-6 as pure diastereomeric white solids.

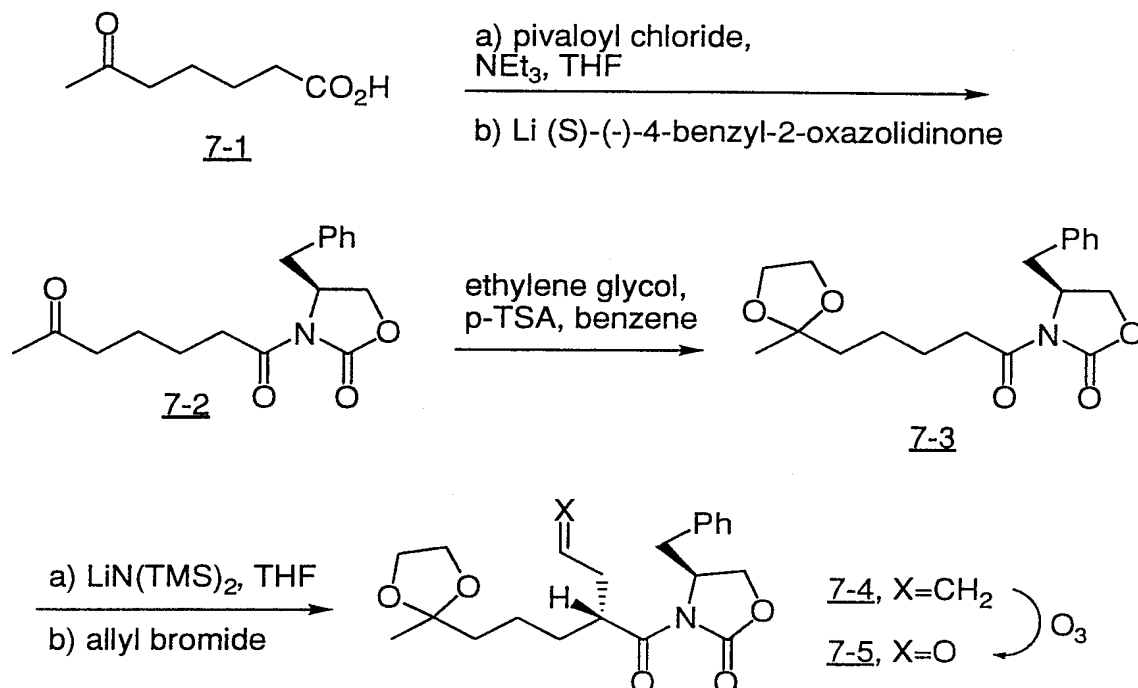
TLC R<sub>f</sub> = 0.32 (isomer A) (10:10:1:1 ethyl acetate/EtOH/water/NH<sub>4</sub>OH).

25    TLC R<sub>f</sub> = 0.28 (isomer B) (10:10:1:1 ethyl acetate/EtOH/water/NH<sub>4</sub>OH).

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD, Isomer A) δ 8.85 (d, J=2Hz, 1H), 8.33 (bs, 1H), 8.00 (m, 2H), 7.78 (m, 1H), 7.44 (d, J=7 Hz, 1H), 6.50 (d, J=7 Hz, 1H), 6.02 (m, 1H), 3.62 (m, 1H), 3.48 (m, 2H), 3.20-1.90 (m, 3H), 2.80-2.60 (m, 4H), 2.13 (m, 1H), 2.00 -1.70 (m, 8H).

30    <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD, Isomer B) δ 8.85 (d, J=2Hz, 1H), 8.33 (bs, 1H), 8.00 (m, 1H), 7.95 (m, 1H), 7.75 (m, 1H), 7.62 (m, 1H), 7.33 (d, J=7 Hz, 1H), 6.43 (d, J=7 Hz, 1H), 5.74 (m, 1H), 3.55 (m, 1H), 3.40 (m, 2H), 3.20-1.95 (m, 2H), 2.72 (m, 2H), 2.58 (m, 3H), 2.23 (m, 1H), 2.00 -1.40 (m, 8H).

## SCHEME 7

1-(4-(S)-benzyl-2-oxo-oxazolidin-3-yl)-heptane-1,6-dione (7-2)

- To a stirred solution of 6-oxo-heptanoic acid **7-1** (100 g, 694 mmol), NEt<sub>3</sub> (111.3 ml, 763.4 mmol) and THF (2000 mL) at -78°C was added pivaloyl chloride (98.7 ml, 763.4 mmol). The mixture was warmed to 0°C for 1.0 h and then recooled to -78°C. To a stirred solution of (S)-(-)-4-benzyl-2-oxazolidinone (136g, 763.4 mmol) and THF (2000 ml) at -78°C was added nBuLi (306 ml, 765 mmol, 2.5M in hexanes) dropwise over 30 minutes. After 20 minutes, the lithium reagent was transferred to the mixed anhydride via cannula. After 20 minutes, the reaction was warmed to 0°C for 1.0h. The mixture was diluted with ethyl acetate, washed with sat. NaHCO<sub>3</sub>, brine, and dried over MgSO<sub>4</sub>. Following evaporative removal of the solvent, the residue was azeotroped with xylenes to give **7-2** as a colorless foam. TLC R<sub>f</sub> = 0.25 (silica, 25% EtOAc/hexanes)



<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.27, (m, 5H), 4.66 (m, 1H), 4.16 (m, 2H), 3.29 (dd, J=3 Hz, 13 Hz, 1H), 2.90 (m, 2H), 2.75 (m, 1H), 2.50 (t, J=7 Hz, 2H), 2.15 (s, 3H), 1.68 (m, 4H).

5 4-(S)-benzyl-3-[5-(2-methyl-[1,3]dioxolan-2-yl)-pentanoyl]-oxazolidin-2-one (7-3)

A mixture of ketone 7-2 (695 mmol), ethylene glycol (59 ml, 1040 mmol), p-TSA (500 mg, 2.713 mmol) and benzene (2000 mL) was heated to reflux with azeotropic removal of water for 12 hours. The reaction mixture was diluted with EtOAc and then washed with sat. NaHCO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>), and concentrated to give 7-3 as a yellow oil.

TLC R<sub>f</sub> = 0.25 (silica, 30% EtOAc/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.26 (m, 5H), 4.67 (m, 2H), 3.94 (s, 4H), 3.29 (m, 1H), 2.95 (m, 2H), 2.76 (m, 1H), 1.71 (m, 4H), 1.50 (m, 2H), 1.32 (s, 3H).

4-(S)-benzyl-3-(R)-{2-[3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-pent-4-enoyl}-oxazolidin-2-one (7-4)

20 To a stirred solution of 7-3 (695 mmol) and THF (2000 mL) at -78°C was added LiN(TMS)<sub>2</sub> (915 mL, 915 mmol, 1.0 M in THF) dropwise over 30 minutes. After 20 minutes, allyl bromide was added. After 20 minutes, the reaction was warmed to 0°C. After 4.0 h, the reaction was diluted with EtOAc, washed with sat. NaHCO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (silica, 25% EtOAc/hexanes) gave 7-4 as a yellow oil.

TLC R<sub>f</sub> = 0.27 (silica, 30% EtOAc/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.25 (m 5H), 5.81 (m, 1H), 5.05 (m, 2H), 4.67 (m, 1H), 4.18 (m, 2H), 3.91 (m, 4H), 3.29 (dd, J=3Hz, 13Hz, 1H), 2.67 (m, 1H), 2.48 (m, 1H), 2.32 (m, 2H), 1.76 (m, 1H) 1.63 (m, 2H), 1.55 (m, 1H), 1.40 (m, 2H), 1.28 (s, 3H).

3-(R)-(4-(S)-benzyl-2-oxo-oxazolidine-3-carbonyl)-6-(2-methyl-[1,3]dioxolan-2-yl)-hexanal (7-5)

To a stirred solution of 7-4 (60 g, 155 mmol), sudan III (20 mg) and CH<sub>2</sub>Cl<sub>2</sub> (1500 mL) at -78°C under argon was bubbled ozone until red solution changed to yellow-orange. The solution was purged with argon for 30 minutes. PPh<sub>3</sub> (61 g, 233 mmol) was added followed by  
5 the removal of the cooling bath. After 2.0 h, the reaction was concentrated. Flash chromatography (silica, 20%-40% EtOAc/hexanes) gave 7-5 as a yellow oil.

TLC R<sub>f</sub> = 0.15 (silica, 50% EtOAc/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.27 (M, 5H), 4.65 (M, 1H), 4.22 (M, 3H), 3.91  
10 (M, 4H), 3.28 (DD, J=3HZ, 13HZ, 1H), 3.05 (M, 1H), 2.78 (M, 2H), 1.69 (M, 3H), 1.50 (M, 3H), 1.29 (S, 3H).

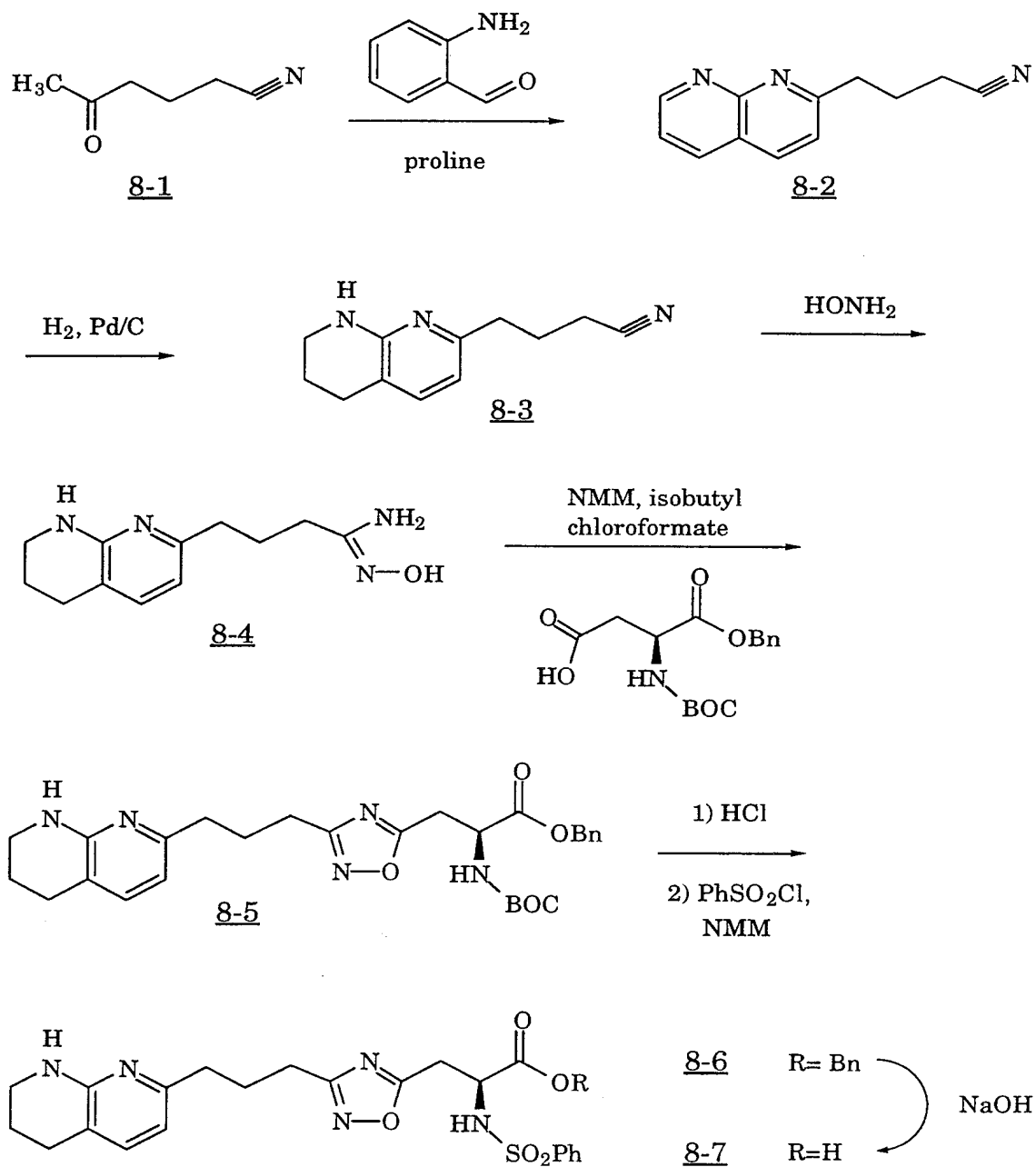
3(S)-(3-Fluorophenyl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid (2-10)

15 The title compound was prepared following the synthetic procedure depicted in Scheme 2, but replacing intermediate 2-5 with the chiral intermediate 7-5, the preparation of which is shown in Scheme 7.

3(S)-(3-Fluorophenyl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-  
20 [1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid (2-11)

The title compound was prepared in a similar fashion as its diastereoisomer 7-6 immediately above, but using the enantiomer of 7-5 prepared in an analogous fashion to that depicted in Scheme 7.

## SCHEME 8

4-[1,8]Naphthyridin-2-yl-butyronitrile (8-2)

A mixture of 5-oxo-hexanenitrile (**8-1**) (5 ml, 43.8 mmol), 2-  
 5 amino-3-formylpyridine (7 g, 57 mmol), proline (5.3 g, 43.8 mmol) and

ethanol (100 mL) was heated at reflux for 12 hours. Following evaporation of the solvent, the residue was chromatographed (silica gel, ethyl acetate) to give 8-2 as a white solid.

TLC  $R_f$  = 0.21 (silica, ethyl acetate).

- 5  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.10 (m, 1H), 8.19 (m, 2H), 7.47 (m, 2H), 3.24 (t, 2H,  $J=7$  Hz), 2.55 (t, 2H,  $J=7$  Hz), 2.39 (m, 2H).

4-(5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl)-butyronitrile (8-3)

- 10 A mixture of 8-2 (14 g, 71 mmol), 10% Pd/C (2 g) and ethanol (200 mL) was stirred under a balloon of hydrogen gas for 1 h. Filtration and evaporation produced 8-3 as a white solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.06 (d, 1H,  $J=7$  Hz), 6.35 (d, 1H,  $J=7$  Hz), 4.76 (br s, 1H), 3.41 (m, 2H), 2.71 (m, 4H), 2.38 (t, 2H,  $J=7$  Hz), 2.08 (m, 3H), 1.85 (m, 2H), 1.80 (m, 1H).

15

2(S)-tert-Butoxycarbonylamino-3-[3-(3-[1,8]naphthyridin-2-yl-propyl)-[1,2,4]oxadiazol-5-yl]-propionic acid benzyl ester (8-5)

- 20 To methanol (20 mL) was added sodium metal (0.86 g, 37 mmol). After 30 minutes, this solution was added to a suspension of hydroxylamine hydrochloride (2.57 g, 37 mmol) in methanol (5 mL). After stirring for 30 min, the mixture was filtered. To this filtrate was added 8-3 (5 g, 24.4 mmol), and the mixture stirred for 24 h at 40°C. An additional portion of hydroxylamine (50 mmol, prepared as above) was then added followed by a further 24 h of stirring. The resulting mixture  
25 was diluted with ethyl acetate, washed with sat.  $\text{NaHCO}_3$ , brine, and dried over  $\text{MgSO}_4$ . Evaporation gave crude amide oxime (8-4).

- To a solution N-BOC-(L)-aspartic acid-alpha benzyl ester (1.5 g, 4.6 mmol) in THF (20 mL) at 0°C was added N-methylmorpholine (0.61 mL, 5.5 mmol) followed by isobutyl chloroformate (0.66 mL, 5.1 mmol). After  
30 30 minutes, a solution of the above crude oxime in DMF (5 mL) was added. The solution was allowed to warm to 25°C and stir for 1 h, then toluene (20 mL) was added and the mixture heated to 110°C, allowing the THF to evaporate. The resulting mixture was heated at reflux for 6 h. Following cooling, the mixture was diluted with ethyl acetate, washed  
35 with sat.  $\text{NaHCO}_3$ , brine, and dried over  $\text{MgSO}_4$ . The residue was

chromatographed (silica gel, 50-60% ethyl acetate/hexanes) to give 8-5 as a yellow oil.

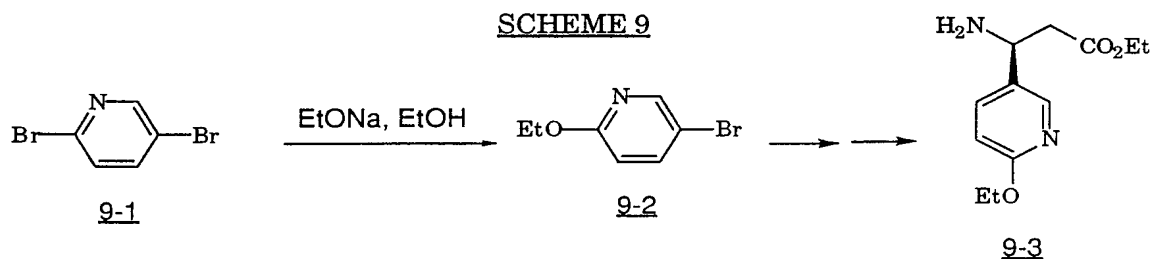
TLC  $R_f$  = 0.63 (silica, ethyl acetate).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (m, 5H), 7.04 (m, 1H), 6.34 (m, 1H), 5.16 (s, 2H), 4.80 (m, 2H), 3.41 (m, 2H), 2.68 (m, 4H), 2.59 (m, 2H), 2.04 (m, 2H), 1.85 (m, 4H), 1.43 (m, 9H).

2(S)-Benzenesulfonylamino-3-[3-(3-[1,8]naphthyridin-2-yl-propyl)-[1,2,4]oxadiazol-5-yl]-propionic acid (8-7)

10 A solution of 4M HCl in dioxane (20 mL) was added to 8-5 (0.7 g, 1.4 mmol). After 30 minutes, the solvent was evaporated to give a white solid. To this solid (0.3 g, 0.64 mmol) was added dichloromethane (10 mL), and NMM (0.7 mL, 6.4 mmol), and the mixture was cooled to 0°C. Phenylsulfonyl chloride (0.081 mL, 0.64 mmol) was added. After 30  
15 minutes, the mixture was diluted with ethyl acetate, washed with sat.  $\text{NaHCO}_3$ , brine, and dried over  $\text{MgSO}_4$ . Evaporation gave the crude ester 8-6, which was dissolved in ethanol (5 mL); sodium hydroxide (0.7 mL, 1 N in water) was added. After 1 hr, the solvent was evaporated, and the residue was chromatographed (silica gel, 25:10:1:1 followed by  
20 15:10:1:1 ethyl acetate /EtOH /water / $\text{NH}_4\text{OH}$ ) to give 8-7 as a white solid. TLC  $R_f$  = 0.48 (10:10:1:1 ethyl acetate/EtOH/water/ $\text{NH}_4\text{OH}$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\Delta$  7.68 (M, 2H), 7.33 (M, 3H), 7.15 (D, 1H,  $J=7$  HZ), 6.39 (D, 1H,  $J=7$  HZ), 3.91 (M, 1H), 3.37 (M, 2H), 3.08 (M, 2H), 2.71 (M, 2H), 2.57 (M, 4H), 1.97 (M, 2H), 1.88 (M, 2H).

25



5-Bromo-2-ethoxypyridine (9-2)

30 Sodium metal (4.87 g, 0.212 mol) was added to ethanol (200 mL) and stirred until completely dissolved. To this solution was added

2,5-dibromopyridine 9-1 (10 g, 0.0424 mol) and the resulting mixture was stirred at reflux for 16 hr. The solvent was removed in vacuo and the residue partitioned between water and EtOAc. After extraction with EtOAc (2x), the organic layer was washed with brine, dried (MgSO<sub>4</sub>) and concentrated to give 9-2 as a red-brown solid which was used as such in the next step.

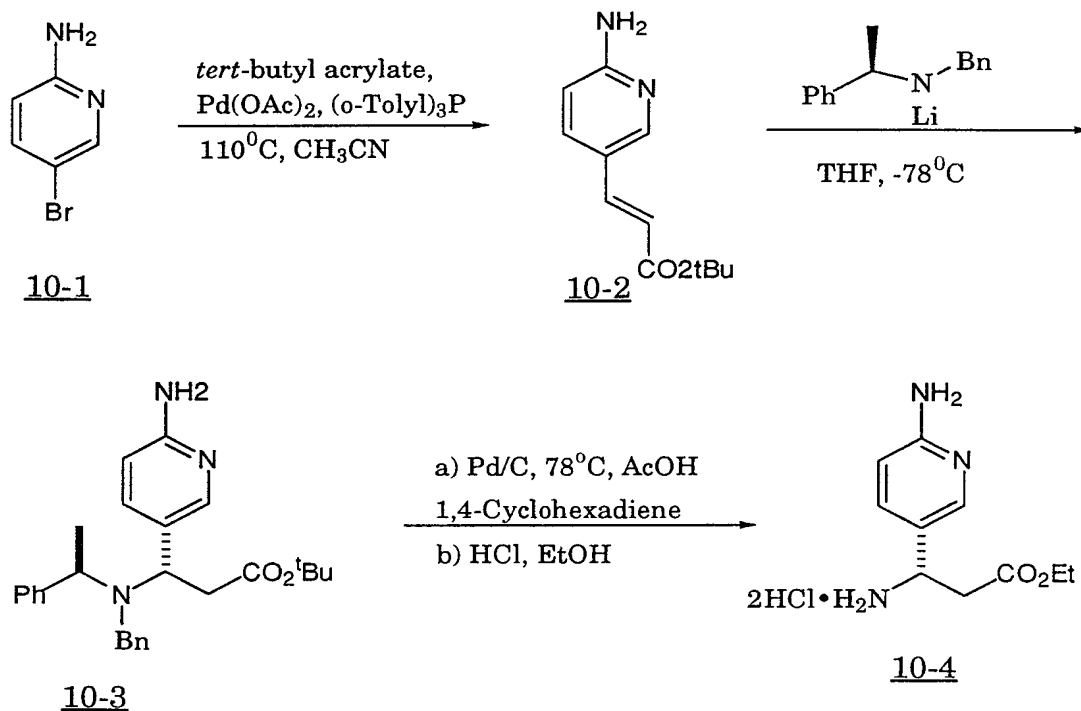
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.4 (3H, t), 4.33 (2H, q), 6.63 (1H, d), 7.62 (1H, dd), 8.19 (1H, d).

### 10 3(S)-(6-Ethoxypyridin-3-yl)-β-alanine ethyl ester (9-3)

The title compound 9-3 was prepared from 9-2 using the procedure described for the synthesis of 19-5 from 19-3.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.25 (3H, t), 1.39 (3H, t), 2.61 (1H, dd), 2.67 (1H, dd), 4.15 (2H, q), 4.34 (2H, q), 4.40 (1H, dd), 6.71 (1H, d), 7.62 (1H, dd), 8.11 (1H, d).

### SCHEME 10



3-(6-Amino-pyridin-3-yl)-acrylic acid *tert*-butyl ester (10-2)

A mixture of 2-amino-5-bromopyridine 10-1 (10 g, 58 mmol), *tert*-butyl acrylate (50 mL, 344 mmol), triethylamine (50 mL, 359 mmol),  
5 tri-*o*-tolylphosphine (3.0 g, 9.8 mmol) and Pd(OAc)<sub>2</sub> (1.0 g, 4.5 mmol) in 150 mL CH<sub>3</sub>CN was purged with argon for 5 min and subsequently refluxed at 110°C for 20 hr. The mixture was then cooled and concentrated. The residue was purified using silica gel flash chromatography (EtOAc/hexanes 1:1) to afford the desired product 10-2  
10 as a solid.

R<sub>f</sub> (silica, EtOAc/hexanes 1:1) = 0.26

3(S)-(6-Amino-pyridin-3-yl)-3-[benzyl-(1(R)-phenylethyl)-aminol]-propionic acid *tert*-butyl ester (10-3)

15 To a cooled (0°C) solution of (R)-(+)-N-benzyl- $\alpha$ -methylbenzylamine (4.0 g, 19 mmol) in 50 mL THF was gradually added n-butyllithium (11.3 mL, 2.5 M, 28.2 mmol) over 5 min. The mixture was stirred for 30 min at 0°C and cooled to  
-78 °C. A solution of 10-2 (2.0 g, 9.4 mmol) in 20 mL THF was gradually  
20 added. After stirring for 40 min at -78 °C, it was treated with NH<sub>4</sub>Cl (sat.) at -78°C, warmed to room temperature and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After solvent evaporation, the residue was purified using silica gel flash chromatography (EtOAc/hexanes 1:2) to afford the  
25 desired product 10-3 as an oil.

R<sub>f</sub> (silica, EtOAc/hexanes 1:1) = 0.28

3(S)-Amino-3-(6-amino-pyridin-3-yl)-propionic acid ethyl ester•2 HCl (10-4)

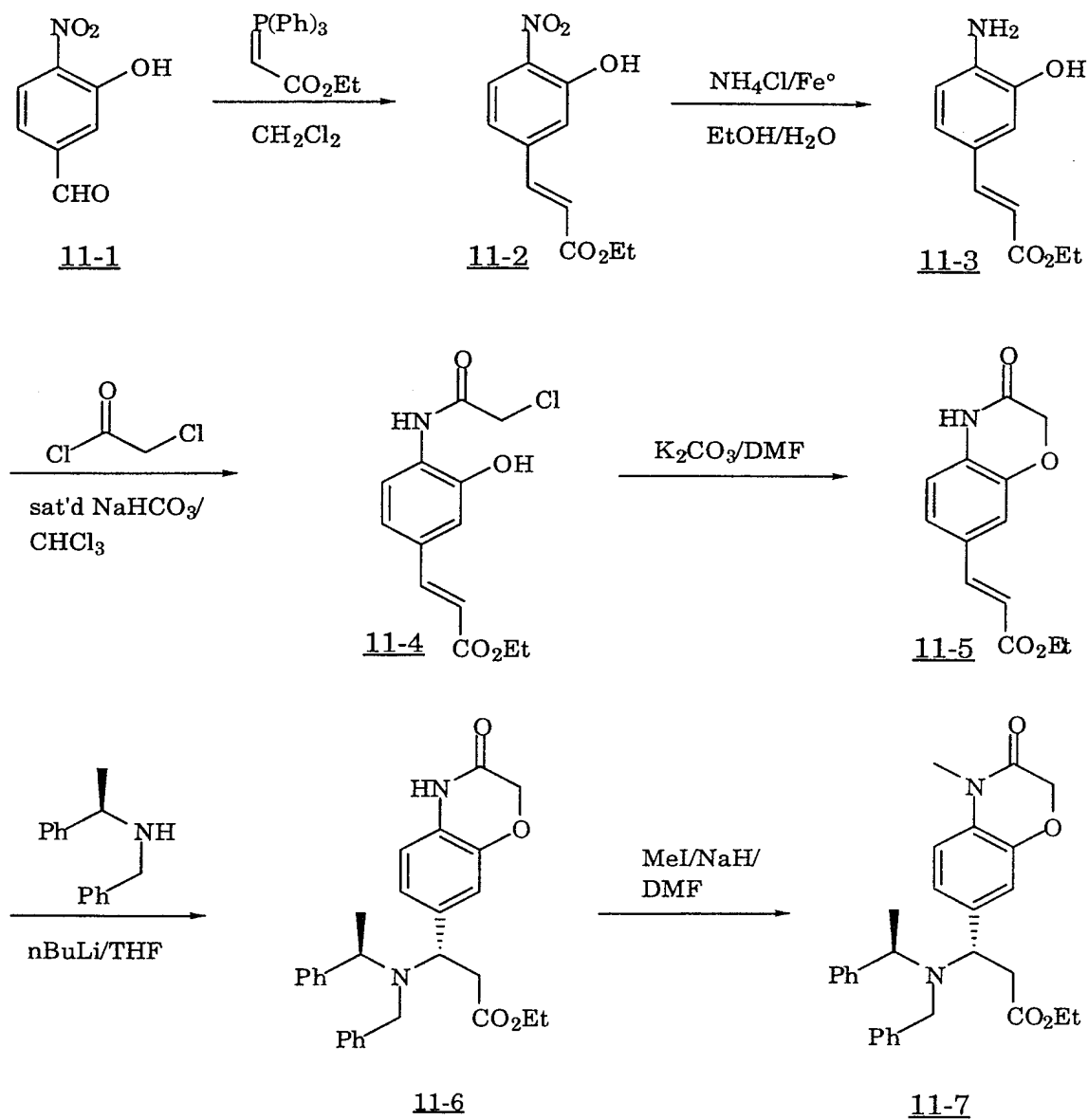
30 A mixture of 10-3 (0.5 g, 1.2 mmol) and 10% Pd/C (0.4 g) in 10 mL AcOH was purged with argon for 5 min and then heated at 78°C. 1,4-Cyclohexadiene (2 mL, 21.1 mmol) was then gradually added. The reaction mixture was stirred for 3 hr and filtered through a celite pad. The solution was concentrated and the residue was purified using silica  
35 gel flash chromatography (EtOAc/MeOH/NH<sub>4</sub>OH 1 :1:0.04) to afford an

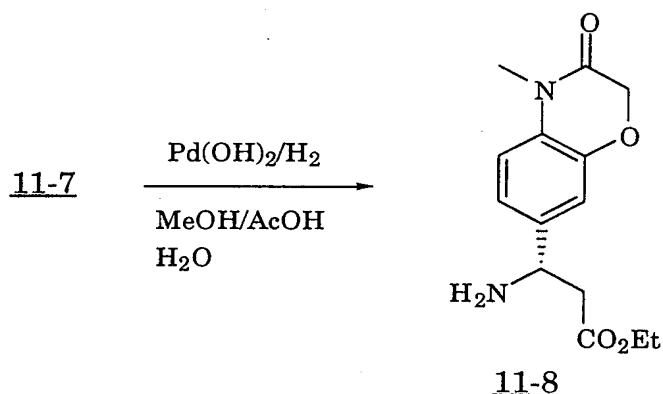
oil. To the oil (1.2 g) in 20 mL EtOH was introduced HCl gas for 10 min. The mixture was stirred 24 hr and then concentrated to afford the desired product 10-4 as the HCl salt.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.11 (d, J=9.6 Hz, 1H), 8.08 (s, 1H), 7.13 (d, J=9.6 Hz, 1H), 4.77 (m, 1H), 4.18 (q, J=6.8 Hz, 2H), 3.22-3.02 (m, 2H), 1.24 (t, J=6.8 Hz, 3H).



## SCHEME 11





3-(3-Hydroxy-4-nitrophenyl)-acrylic acid ethyl ester (11-2)

- To a stirred solution of aldehyde 11-1 (20.28 g, 132.5 mmol) in  
 5  $\text{CH}_2\text{Cl}_2$  (400 mL) at room temperature was added  
 (carbethoxymethylene)triphenylphosphorane (46.12 g, 132.5 mmol) over  
 a 10 min period. The resulting orange solution was stirred at room  
 temperature for 2 h. The solution was concentrated to one-fourth its  
 volume. Flash chromatography (silica gel; 30:70 EtOAc/hexanes) gave  
 10 the title compound 11-2 as a bright yellow solid.  
 TLC Rf = 0.75 (25:75 EtOAc/hexanes)  
 $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (d, 1H), 7.60 (d, 1H), 7.15 (dd, 1H), 6.54  
 (d, 1H), 4.30 (q, 2H), 1.36 (t, 3H).

15 3-(4-Amino-3-hydroxyphenyl)-acrylic acid ethyl ester (11-3)

- To a stirred suspension of 11-2 (4.64 g, 19.6 mmol),  $\text{NH}_4\text{Cl}$   
 (524 mg, 9.8 mmol), EtOH (140 mL) and  $\text{H}_2\text{O}$  (70 mL) was added iron dust  
 (2.72 g, 48.9 mmol). The resulting yellow suspension was refluxed for  
 1.5 h., and then the solution was filtered while hot through celite. The  
 20 filtrate was concentrated and the residue was partitioned between EtOAc  
 and brine. The layers were separated and the EtOAc layer dried  
 ( $\text{Na}_2\text{SO}_4$ ) and concentrated to give 11-3 which was used without further  
 purification in the next step.  
 TLC Rf = 0.2 (25:75 EtOAc/hexanes)  
 25  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (d, 1H), 7.00 (m, 2H), 6.68 (d, 1H), 6.20  
 (d, 1H), 4.26 (q, 2H), 4.10 (b, 2H), 1.33 (t, 3H).

3-[4-(2-Chloroacetyl-amino)-3-hydroxyphenyl]acrylic acid ethyl ester  
(11-4)

To a stirred solution of 11-3 (3.38 g, 16.3 mmol) in CHCl<sub>3</sub> (80 mL) was added saturated NaHCO<sub>3</sub> (50 mL) and it was then chilled to 0°C. A solution of chloroacetyl chloride (1.94 mL, 24.4 mmol) in CHCl<sub>3</sub> (30 mL) was added dropwise to the chilled biphasic. Upon addition completion, the reaction was stirred at 0°C for 1 h. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give 11-4 which was used without further purification in the next step.

TLC R<sub>f</sub> = 0.4 (25:75 EtOAc/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.33 (s, 1H), 9.58 (s, 1H), 8.02 (d, 1H), 7.51 (d, 1H), 7.19 (d, 1H), 7.12 (s, 1H), 6.39 (d, 1H), 4.42 (s, 2H), 4.17 (q, 2H), 1.25 (t, 3H).

3-(3-Oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl) acrylic acid ethyl ester  
(11-5)

To a stirred solution of 11-4 (4.28 g, 15.0 mmol) in DMF (50 mL) was added K<sub>2</sub>CO<sub>3</sub> (4.50 g, 32.6 mmol). The resulting suspension was heated to 50°C for 12 h., after which time the reaction was concentrated. The residue was partitioned between saturated NaHCO<sub>3</sub> and EtOAc and extracted twice with EtOAc. The combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Flash chromatography (silica gel; 25:75 EtOAc/hexanes) yielded 11-5 as a beige solid.

TLC R<sub>f</sub> = 0.5 (25:75 EtOAc/hexanes).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.91 (s, 1H), 7.54 (d, 1H), 7.37 (s, 1H), 7.31 (d, 1H), 6.90 (d, 1H), 6.51 (d, 1H), 4.60 (s, 2H), 4.16 (q, 2H), 1.24 (t, 3H).

3-(R)-[Benzyl-(1-phenylethyl)-aminol-3-(S)-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl) propionic acid ethyl ester (11-6)

To a stirred solution of (R)-(+)-N-benzyl-α-methylbenzylamine (5.43 g, 25.7 mmol) and anhydrous THF (75 mL) at

0°C was added butyllithium (10.3 mL, 2.5 M/hexanes, 25.7 mmol) via syringe. The violet-red solution was stirred at 0°C for 15 minutes and then cooled to -78°C. A solution of 11-5 (2.12 g, 8.6 mmol) in anhydrous THF (50 mL) was added via syringe, and the resulting brown solution  
5 was stirred at -78°C for 30 minutes. The brown solution was quenched with saturated NH<sub>4</sub>Cl, the mixture then warmed to room temperature and extracted twice with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Flash chromatography (silica gel; 15:85 to 25:75 EtOAc/hexanes) yielded 11-6 as  
10 a white foam.

TLC R<sub>f</sub> = 0.25 (25:75 EtOAc/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.89 (s, 1H), 7.32 (m, 10H), 7.10 (m, 2H), 6.91 (d, 1H), 4.62 (s, 2H), 4.39 (m, 1H), 4.13 (q, 2H) 3.96 (m, 1H), 3.68 (s, 2H), 2.56 (m, 2H), 1.28 (m, 6H).

15

3-(R)-[Benzyl-(1-phenylethyl)-aminol-3-(S)-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl) propionic acid ethyl ester (11-7)

To a stirred suspension of NaH (65 mg, 60%, 1.6 mmol) in DMF (5 mL) under argon was added a solution of 11-6 (650 mg, 1.4 mmol)  
20 in DMF (10 mL) via syringe. This yellow solution was stirred at room temperature for 30 minutes. Iodomethane (500 µL, 8.0 mmol) was added and the solution then stirred at room temperature for an additional 30 minutes. The reaction was quenched with saturated NaHCO<sub>3</sub>. The aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined  
25 organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Flash chromatography (silica gel; 25:75 EtOAc/hexanes) afforded 11-7 as a clear oil.

TLC R<sub>f</sub> = 0.6 (25:75 EtOAc/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.30 (m, 10H), 7.06 (m, 2H), 6.91 (d, 1H), 4.62  
30 (s, 2H), 4.39 (m, 1H), 4.13 (q, 2H) 3.96 (m, 1H), 3.68 (s, 2H), 3.35 (s, 3H), 2.56 (m, 2H), 1.26 (m, 6H).

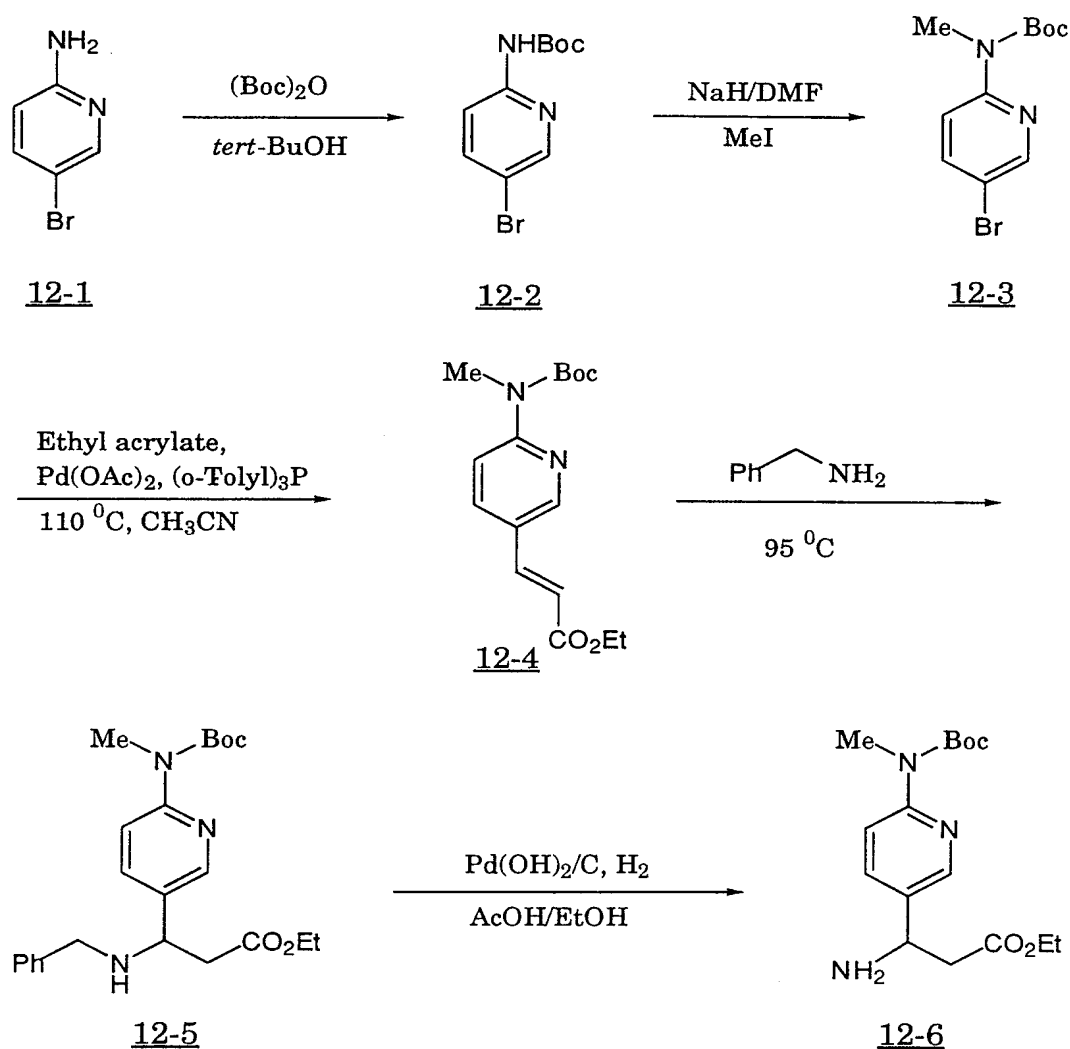
3-(S)-Amino-3-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl) propionic acid ethyl ester (11-8)

A stirred solution of 11-7 (581 mg, 1.2 mmol), MeOH (10 mL), AcOH (1.0 mL), and H<sub>2</sub>O (0.3 mL) was degassed with argon for 5 minutes. Pd(OH)<sub>2</sub> (581 mg) was added and the reaction was placed under 1 atm of H<sub>2</sub> for 2.5 h. The reaction was diluted with EtOAc and  
5 filtered through celite. The filtrate was concentrated to yield 11-8 as a clear oil.

TLC R<sub>f</sub> = 0.3 (5:95 MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.04 (m, 2H), 6.93 (dd, 1H), 4.61 (s, 2H), 4.39  
10 (m, 1H), 4.13 (q, 2H), 3.37 (b, 2H), 3.35 (s, 3H), 2.69 (m, 2H), 1.24 (t, 3H).

## SCHEME 12

2-tert-Butoxycarbonylamino-5-aminopyridine (12-2)

- A solution of 2-amino-4-bromopyridine **12-1** (10.1 g, 58.4 mmol) in 150 mL of melted *t*-BuOH was treated with di-*tert*-butyl dicarbonate (14.0 g, 64.2 mmol). After the solution was stirred for 12 hr, the solvent was evaporated. The residue was purified using silica gel flash chromatography ( $\text{CHCl}_3$ /hexanes, 5:1) to afford the desired product **12-2** as a solid.
- $R_f$  (silica, 100%  $\text{CHCl}_3$ ) = 0.56

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.82 (bs, 1H), 8.38 (d, 1H), 8.78 (d, 1H), 7.78 (dd, 1H), 1.55 (s, 9H).

2-(tert-Butoxycarbonyl-methyl-amino)-5-aminopyridine (12-3)

5 To a solution of 12-2 (6.0 g, 22.0 mmol) in 50 mL DMF at  $0^\circ\text{C}$  was added NaH gradually. After the mixture was stirred for 40 min,  $\text{CH}_3\text{I}$  (3.4 g, 24.0 mmol) was added in one portion. The reaction mixture was stirred for 5 hr, treated with 300 mL water and extracted three times with ethyl ether. The combined organic layers were washed with brine  
10 and dried over  $\text{Na}_2\text{SO}_4$ . After solvent removal, the residue was purified by silica gel flash chromatography ( $\text{CHCl}_3$ /hexanes 6:1) to afford the desired product 12-3 as a solid.  
 $R_f$  (silica, 100%  $\text{CHCl}_3$ ) = 0.40  
 $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.40 (dd, 1H), 7.68 (m, 2H), 3.36 (s, 3H), 1.55  
15 (s, 9H).

3-[6-(tert-Butoxycarbonyl-methyl-amino)-pyridin-3-yl]-acrylic acid ethyl ester (12-4)

A mixture of 12-3 (6.0 g, 20.9 mmol), ethyl acrylate (6.3 mL, 62.7 mmol), triethylamine (17 mL, 125.5 mmol), tri-*o*-tolylphosphine (1.3 g, 6.2 mmol) and  $\text{Pd}(\text{OAc})_2$  (0.5 g, 2.1 mmol) in 50 mL  $\text{CH}_3\text{CN}$  was  
20 purged with argon for 5 min and subsequently refluxed at  $110^\circ\text{C}$  for 20 hr. The mixture was cooled and concentrated. The residue was purified using silica gel flash chromatography (EtOAc/hexanes 1:3) to afford the  
25 desired product 12-4 as an oil.  
 $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47 (bs, 1H), 7.82 (m, 2H), 7.64 (d, 1H), 6.42 (d, 1H), 4.27 (q, 2H), 3.43 (s, 3H), 1.54 (s, 9H), 1.34 (t, 3H).

3-Benzylamino-3-[6-(tert-butoxycarbonyl-methyl-amino)-pyridin-3-yl]-propionic acid ethyl ester (12-5)

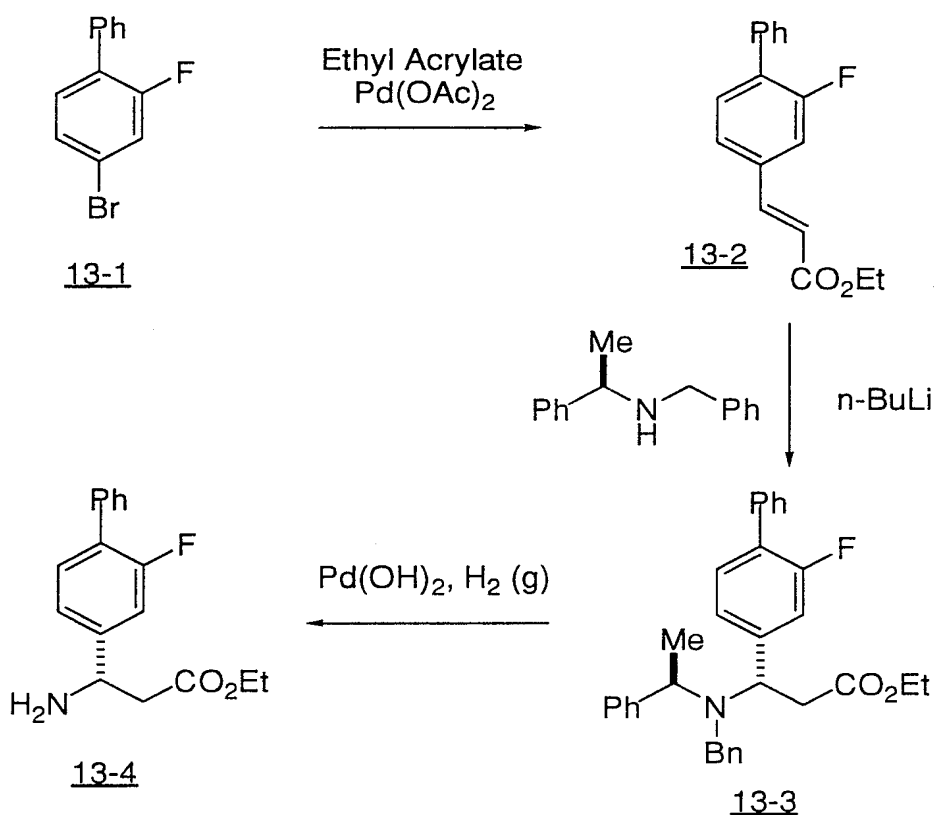
30 A mixture of 12-4 (1.7 g, 5.6 mmol) and benzylamine (8 mL, 73.2 mmol) was heated in a sealed-tube at  $95^\circ\text{C}$  for 24 hr. The crude reaction mixture was purified using silica gel flash chromatography (EtOAc/hexanes 1:3 to 1:1) to afford the desired product 12-5 as an oil.

R<sub>f</sub> (silica, EtOAc/hexanes 1:1) = 0.63.

3-Amino-3-[6-(*tert*-butoxycarbonyl-methyl-amino)-pyridin-3-yl]-propionic acid ethyl ester (12-6)

- 5 A mixture of 12-5 (1.5 g 3.6 mmol), 20% Pd(OH)<sub>2</sub>/C (0.3 g), AcOH (5.5 mL) and EtOH (50 mL) was purged with argon 3 times under vacuum. The reaction mixture was stirred under balloon hydrogenation condition for 16 hr and filtered through a celite pad. After solvent removal, the desired product 12-6 was obtained as the acetate salt.
- 10 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.38 (d, 1H), 7.70 (m, 2H), 4.50 (dd, 1H), 4.15 (q, 2H), 3.40 (s, 3H), 2.80 (m, 2H), 1.25 (t, 3H).

SCHEME 13



- 15 3-(2-Fluoro-biphenyl-4-yl)-acrylic acid ethyl ester (13-2)



A solution of 2-fluoro-4-bromobiphenyl 13-1 (7.5 gm, 31.8 mmol), ethyl acrylate (4.3 mL), Pd(OAc)<sub>2</sub> (0.714 gm, 3.2 mmol), tri-*o*-tolylphosphine (1.94 gm, 1.5 mmol) and triethylamine (12 mL) was heated to 100°C in a sealed tube for 12 h. The reaction was cooled to room temperature and diluted with dichloromethane (40 mL). The organic solution was washed with 10% aq. citric acid (20 mL), satd. aq. NaHCO<sub>3</sub>, and brine (20 mL). The organic solution was dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography (95:5 to 90:10 hexanes/EtOAc) to give the acrylate ester 13-2 as a white solid.

TLC Rf = 0.44 (10% ethyl acetate/hexanes).

3-[Benzyl-(1(R)-phenylethyl)-aminol-3-(2-fluoro-biphenyl-4-yl)-propionic acid ethyl ester (13-3)

A cooled (0°C) solution of N-benzyl-(R)- $\alpha$ -methylbenzylamine (8.9 mL, 42.6 mmol) in THF (100 mL) was treated with *n*-butyllithium (26.6 mL of a 1.6 M soln in hexanes; 42.6 mmol). After stirring for 10 min, the purple solution was cooled to -78°C and treated with a solution of ester 13-2 (5.76 g, 21.3 mmol) in THF (10 mL). After stirring for 20 min, the solution was quenched with satd aq NH<sub>4</sub>Cl soln (5 mL), and the cold bath removed. The reaction mixture was diluted with Et<sub>2</sub>O (100 mL), and washed with 10% aq citric acid (50 mL), satd aq NaHCO<sub>3</sub> (50 mL), 5% aq acetic acid (30 mL), 10% aq K<sub>2</sub>CO<sub>3</sub> (50 mL), and brine (50 mL). The solution was dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography (90:10 hexanes/EtOAc) to give adduct 13-3.

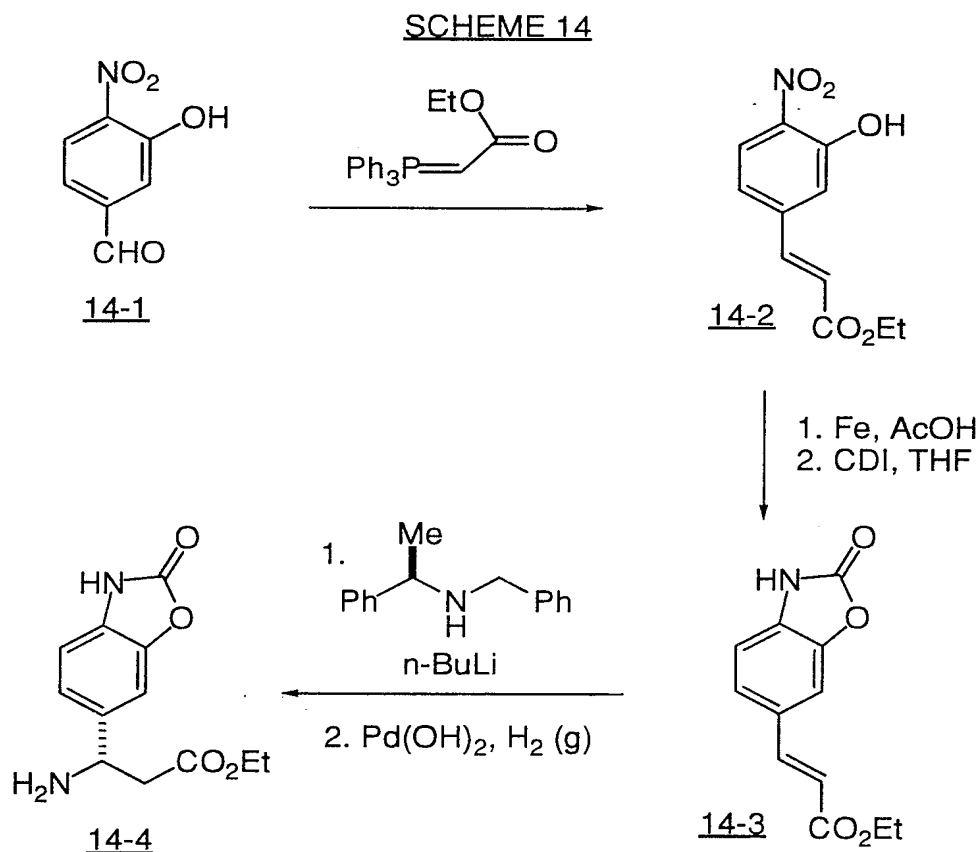
TLC Rf = 0.48 (10% ethyl acetate/hexanes).

3-Amino-3-(2-fluoro-biphenyl-4-yl)-propionic acid ethyl ester (13-4)

A solution of the dibenzylamine 13-3 (5.65 gm, 11.75 mmol) in EtOH/HOAc (90/10 mL) was purged with argon and treated with Pd(OH)<sub>2</sub> (3 g) and placed under 1 atm of H<sub>2</sub> gas for 12 h. Additional portions (2.5 g) of Pd(OH)<sub>2</sub> were added after 24 h, 48 h and 144 h. The reaction mixture was purged with argon, filtered through Celite, and the filtrate dissolved in aq HCl (pH=1). The aqueous solution was

washed with EtOAc, neutralized with satd aq NaHCO<sub>3</sub>, and extracted with EtOAc (3 x 30 mL). The combined organic solutions were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give the desired product 13-4.

- 5 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.41 (m, 8H), 4.10 (m, 1H), 4.06 (m, 2H), 2.73 (m, 2H), 1.18 (m, 3H) ppm.



10 3-(3-Hydroxy-4-nitro-phenyl)-acrylic acid ethyl ester (14-2)

- To a solution of aldehyde 14-1 (15.0 g, 98.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) was slowly added carboethoxymethylenetriphenylphosphorane (34.1 g, 98.0 mmol). The orange solution was stirred for 12 h at ambient temperature. The solution was concentrated to a paste and purified by  
 15 flash chromatography (10% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) to give 14-2 as a yellow solid. TLC R<sub>f</sub> = 0.51 (30% ethyl acetate/hexanes).

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 8.08 (d, J=8.4 Hz, 1H), 7.63 (d, J=16.2 Hz, 1H), 7.35 (d, J=1.5 Hz, 1H), 7.27 (dd, J=8.4, 1.5 Hz, 1H), 6.65 (d, J=15.9 Hz, 1H), 4.25 (q, J=7.2 Hz, 2H), 1.32 (t, J=6.9 Hz, 3H) ppm.

5     3-(2-Oxo-2,3-dihydro-benzoxazol-6-yl)-acrylic acid ethyl ester (14-3)

To a solution of the nitrophenol 14-2 (12.0 g, 57.4 mmol) in warm (70°C) AcOH/H<sub>2</sub>O (200 mL) was added iron dust (9.61 g, 172.2 mmol). The brown heterogeneous mixture was stirred for 30 min at 70-80°C. The mixture was filtered hot through Celite, and the Celite bed  
10     washed with EtOAc (2 x 200 mL). The filtrate was cautiously neutralized with satd aq NaHCO<sub>3</sub> (3 x 100 mL). The solution was dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) give an orange solid (9.6 g, 81%). A portion of this solid (4.5 g, 21.7 mmol) was dissolved in THF (150 mL)  
15     and treated with 1,1-carbonyldiimidazole (3.87 g, 23.8 mmol) and the solution was stirred at ambient temperature for 24 h. The solution was diluted with EtOAc (100 mL) and washed with 10% HCl (50 mL) and brine (50 mL). The solution was dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography (5%  
20     MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to give 14-3 as a yellow solid.

TLC R<sub>f</sub> = 0.49 (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>).

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.77 (d, J=15.9 Hz, 1H), 7.55 (s, 1H), 7.41 (d, J=8.4 Hz, 1H), 7.09 (d, J=8.1 Hz, 1H), 6.47 (d, J=15.9 Hz, 1H), 4.22 (q, J=7.2 Hz, 2H), 1.31 (t, J=7.2 Hz, 3H) ppm.

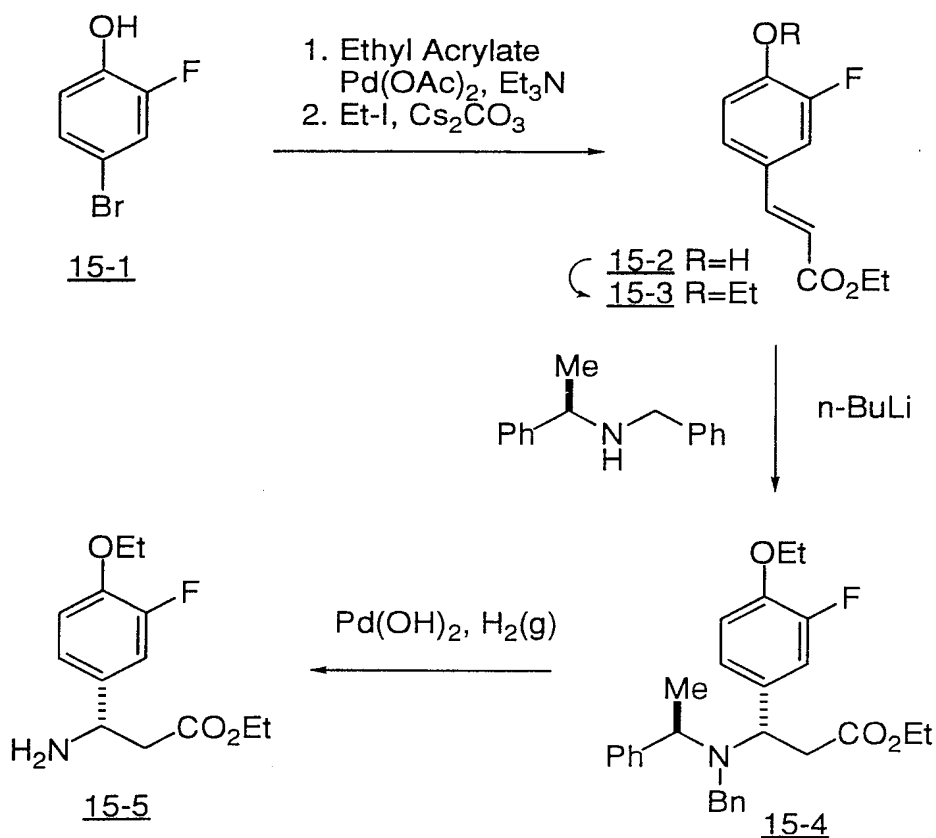
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3S-Amino-3-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-propionic acid ethyl ester (14-4)

A solution of N-benzyl-α-(R)-methylbenzylamine (4.08 g, 19.3 mmol) in THF (120 mL) at 0°C was treated with n-BuLi (7.72 mL of a 2.5  
30     M soln in hexanes). The resulting solution was stirred at 0°C for 30 min and then cooled to -78°C. A solution of acrylate 14-3 (1.5 g, 6.43 mmol) in THF (20 mL) was added. After stirring for 15 min at -78°C, satd aq NH<sub>4</sub>Cl soln (25 mL) was added and the cold bath removed. The mixture was warmed to room temperature, and extracted with Et<sub>2</sub>O (2 x 40 mL).

- The combined organic extracts were washed with brine (30 mL), dried over  $\text{MgSO}_4$ , filtered, and concentrated. The residue was purified by flash chromatography (30% ethyl acetate/hexanes) to give 2.74 g of the  $\beta$ -aminoester as a yellow oil. The aminoester was dissolved in
- 5 EtOH/ $\text{H}_2\text{O}$ / $\text{AcOH}$  (54 mL/4.8 mL/1.2 mL), degassed with argon, and treated with  $\text{Pd}(\text{OH})_2$  (2.74 g). The mixture was placed under 1 atm of  $\text{H}_2$ . After stirring for 18 h, the mixture was diluted with EtOAc, and filtered through Celite. The filtrate was concentrated to give ester 14-4 as an off-white solid.
- 10 TLC  $R_f$  = 0.10 (5% MeOH/ $\text{CH}_2\text{Cl}_2$ ).  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.34 (s, 1H), 7.26 (dd,  $J=1.2, 8.1$  Hz, 1H), 7.12 (d,  $J=8.1$  Hz, 1H), 4.65 (t,  $J=7.2$  Hz, 1H), 4.13 (q,  $J=6.9$  Hz, 2H), 2.98 (m, 2H), 1.20 (t,  $J=7.2$  Hz, 3H) ppm.

## SCHEME 15



3-(4-Hydroxy-3-fluorophenyl)-acrylic acid ethyl ester (15-2)

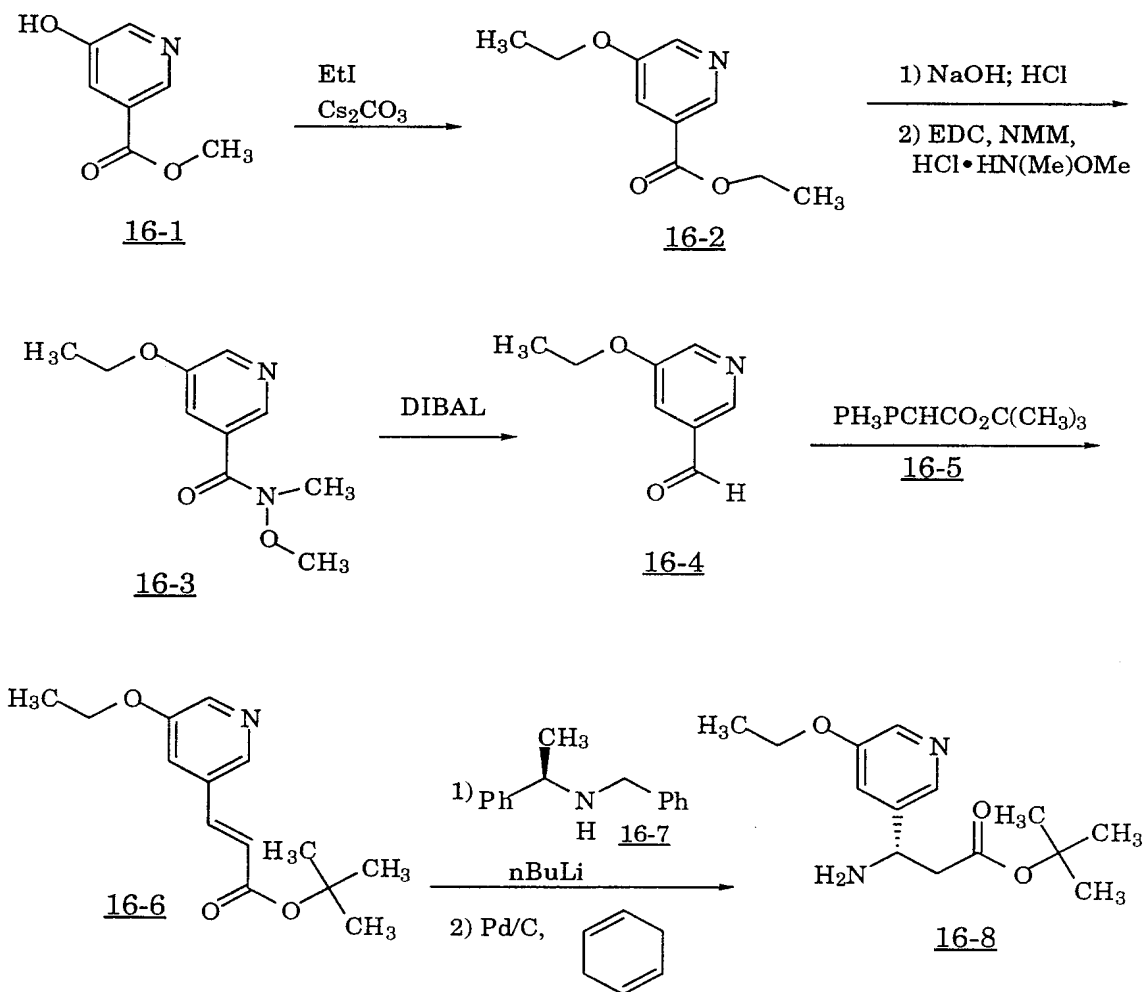
A solution of 2-fluoro-4-bromophenol 15-1 (50 g, 261.8 mmol), ethyl acrylate (34 mL), Pd(OAc)<sub>2</sub> (2.5 g), tri-*o*-tolylphosphine (5 g) and  
5 triethylamine (83 mL) was heated to 100°C in a sealed tube for 12 h. The reaction was cooled to room temperature and diluted with dichloromethane (100 mL). The organic solution was washed with 10% aq. citric acid (40 mL), satd aq NaHCO<sub>3</sub>, and brine (40 mL). The organic solution was dried over MgSO<sub>4</sub>, filtered and concentrated. The residue  
10 was purified by flash chromatography (50:50 hexanes/EtOAc to 100% EtOAc) to give acrylic acid 15-2 as a white solid.  
TLC Rf = 0.45 (50% ethyl acetate/hexanes).

3-[Benzyl-(1(R)-phenylethyl)-amino]-3-(4-ethoxy-3-fluorophenyl)-propionic acid ethyl ester (15-4)

To a stirred solution of 15-2 (49.25 gm, 234.5 mmol) in DMF (600 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (84.1 gm, 257.9 mmol) and ethyl iodide (18.8 mL, 234.5 mmol). After stirring for 12 h at room temperature, the reaction mixture was diluted with EtOAc (1L) and washed with water (6  
20 x 300 mL), 10% aq. citric acid (200 mL), satd. aq. NaHCO<sub>3</sub> (200 mL), and brine (300 mL). The organic solution was dried over MgSO<sub>4</sub>, filtered, and concentrated to give 52.9 g (95%) of the product 15-3 as an orange oil which crystallized upon standing. A cooled (0°C) solution of N-benzyl-(R)- $\alpha$ -methylbenzylamine (71 mL, 339.4 mmol) in THF (650 mL) was  
25 treated with n-butyllithium (212 mL of a 1.6 M soln in hexanes; 339.4 mmol). After stirring for 10 min, the purple solution was cooled to -78°C and treated with a solution of ester 15-3 (53.8 g, 226.3 mmol) in THF (100 mL). After stirring for 20 min, the solution was quenched with satd aq NH<sub>4</sub>Cl soln (50 mL), and the cold bath removed. The reaction mixture  
30 was diluted with Et<sub>2</sub>O (1000 mL), and washed with 10% aq citric acid (300 mL), satd aq NaHCO<sub>3</sub> (300 mL), 5% aq acetic acid (300 mL), 10% aq K<sub>2</sub>CO<sub>3</sub> (300 mL), and brine (200 mL). The solution was dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography (85:15 hexanes/EtOAc) to give the adduct 15-4.  
35 TLC Rf = 0.39 (25% ethyl acetate/hexanes).

3-Amino-3-(4-Ethoxy-3-fluorophenyl)-propionic acid ethyl ester (15-5)

- A solution of the dibenzylamine 15-4 (30.0 gm, 66.8 mmol) in EtOH/HOAc (340/30 mL) was purged with argon and treated with
- 5 Pd(OH)<sub>2</sub> (6 g) and placed under 1 atm of H<sub>2</sub> for 12 h. Additional portions (2.5 g) of Pd(OH)<sub>2</sub> were added after 24 h and 48 h. The reaction mixture was purged with argon, filtered through Celite, and the filtrate collected. The filtrate was concentrated to yield the desired amine 15-5.  
<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.19 (m, 3H), 4.62 (m, 1H), 4.07 (m, 4H),  
 10 2.99 (m, 2H), 1.39 (m, 3H) 1.18 (m, 3H) ppm.

SCHEME 16

5-Ethoxy-nicotinic acid ethyl ester (16-2)

A mixture of 3-hydroxy-nicotinic acid methyl ester 16-1 (15 g, 90.8 mmol), ethyl iodide (14.5 ml, 181.6 mmol), cesium carbonate (29.5 g, 90.8 mmol) and DMF (150 mL) was stirred at ambient temperature for 3 hours. The reaction mixture was diluted with Et<sub>2</sub>O and then washed with 10% K<sub>2</sub>CO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>), and concentrated to give the ester 16-2 as a red oil.

TLC R<sub>f</sub> = 0.52 (silica, 75% EtOAc/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.82 (s, 1H), 8.46 (s, 1H), 7.75 (s, 1H), 4.40 (q, 2H, J=7Hz), 4.12 (q, 2H, J=7Hz), 1.43 (m, 6H).

5-Ethoxy-N-methoxy-N-methyl-nicotinamide (16-3)

To a solution of 16-2 (15 g, 72 mmol) in EtOH (100 mL) was added 1N NaOH (80 ml, 80 mmol). After stirring for 1 h, the solvents were evaporated and the residue was dissolved in 1N HCl (80 ml, 80 mmol) and then concentrated, azeotroped with CH<sub>3</sub>CN to give the crude acid. The crude acid was suspended in DMF (200 mL) and then treated with HCl•HN(Me)OMe (13.9 g, 144 mmol), EDC (15.1g, 79.2 mmol), HOBT (9.6g, 72 mmol) and NMM (60 mL, 576 mmol). The mixture was stirred for 18 hours and then concentrated. The residue was dissolved in ethyl acetate, washed with 10% K<sub>2</sub>CO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>), and concentrated to give amide 16-3 as a brown oil.

TLC R<sub>f</sub> = 0.30 (silica, 70:25:5 chloroform/ ethyl acetate/ MeOH)

5-Ethoxy-pyridine-3-carbaldehyde (16-4)

To a stirred solution of 16-3 (14.0 g, 66.5 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (200 mL) at -78°C under argon was added DIBAL (1.0M hexanes, 90ml) dropwise over 30 minutes. After 30 minutes, the solution was warmed to 0°C for 1 hour. The reaction was quenched with 100 ml 1.0M Rochelle's salt, stirred for 1.0 hour and then extracted with Et<sub>2</sub>O. The organic layer was dried (MgSO<sub>4</sub>), and then concentrated to give the aldehyde 16-4 as a brown oil.

TLC R<sub>f</sub> = 0.32 (silica, 70:25:5 chloroform/ethyl acetate/MeOH)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.10 (s, 1H), 8.65 (s, 1H), 8.55 (s, 1H), 7.59 (s, 1H), 4.14 (q, 2H, J=7Hz), 1.43 (t, 3H, J=7Hz).

3-(5-Ethoxy-pyridin-3-yl)-acrylic acid *tert*-butyl ester (16-6)

A mixture of 16-4 (8.0 g, 51.6 mmol), 16-5 (20 g, 54.2 mmol), and benzene (150 mL) was heated to reflux for 30 minutes. The mixture  
5 was diluted with Et<sub>2</sub>O and then washed with 10% K<sub>2</sub>CO<sub>3</sub>, brine and dried (MgSO<sub>4</sub>). Following evaporative removal of the solvent, the residue was chromatographed (silica gel, 30% EtOAc/hexanes) to give 16-6 as a yellow solid.

TLC R<sub>f</sub> = 0.41 (silica, 70:25:5 chloroform/ ethyl acetate/ MeOH)

10 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.31 (m, 2H), 7.55 (d, 1H, J=16Hz), 7.27 (s, 1H), 6.40 (d, 1H, J=16Hz), 4.10 (q, 2H, J=7Hz), 1.54 (s, 9H), 1.44 (m, 3H).

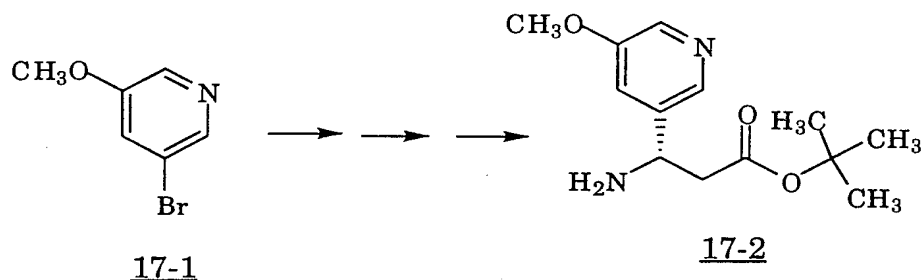
3(S)-Amino-3-(5-ethoxy-pyridin-3-yl)-propionic acid *tert*-butyl ester (16-8)

To a stirred solution of 16-7 (500mg, 2.38mmol) and THF at  
15 0°C was added nBuLi (2.5 M THF, 0.95 ml) dropwise. After 20 minutes, the solution was cooled to -78°C and 16-6 (500mg, 1.98 mmol), dissolved in 3 ml THF, was added. After 15 minutes, the reaction was quenched with sat. NH<sub>4</sub>Cl followed by the removal of the cooling bath. The solution was extracted with ethyl acetate. The organic portion was washed with  
20 brine, dried (MgSO<sub>4</sub>) and concentrated. The residue was dissolved in acetic acid (14 ml) and the solution was purged with argon for 30 minutes. 10% Pd/C (1.0 g) was added and the mixture was heated to 80°C. 1,4-Cyclohexadiene (6 ml) was added dropwise maintaining an internal temperature between 80°C and 90°C. After 5.0 hours, the  
25 mixture was filtered through a celite pad, concentrated and then azeotroped with toluene. The residue was chromatographed (silica gel, 5% [10:10:1 EtOH/NH<sub>4</sub>OH/H<sub>2</sub>O]/ 70:25:5 chloroform/ ethyl acetate/ MeOH) to give 16-8 as a yellow solid.

30 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.18 (m, 2H), 7.25 (s, 1H), 4.41 (m, 1H), 4.08 (q, 2H, J=7Hz), 2.59 (m, 2H), 1.87 (s, 2H), 1.40 (m, 12H).



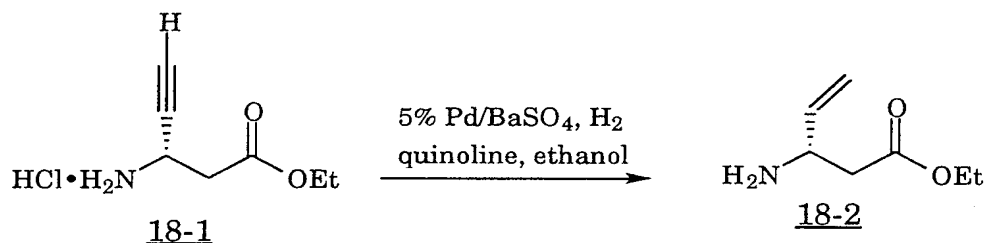
## SCHEME 17



3(S)-Amino-3-(5-methoxy-pyridin-3-yl)-propionic acid *tert*-butyl ester (17-2)

- 3-Bromo-5-methoxy-pyridine **17-1** (prepared as described in *J. Org. Chem.* 1990, 55, 69) was converted into **17-2** utilizing the procedure described for the conversion of **19-2** to **19-5**. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 8.20 (d, 1H, J=3Hz), 8.18 (d, 1H, J=2Hz), 7.50 (s, 1H), 4.51 (m, 1H), 3.90 (s, 3H), 2.87 (m, 2H), 1.37 (m, 9H).

## SCHEME 18



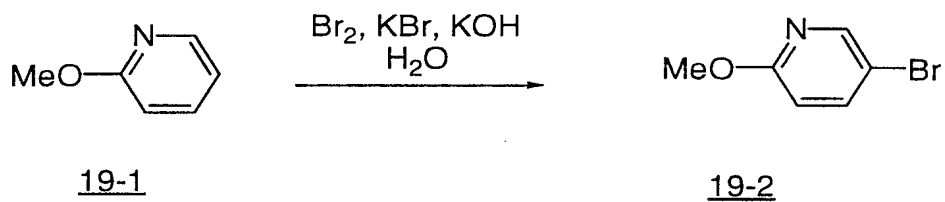
10

3-Amino-pent-4-enoic acid ethyl ester (18-2)

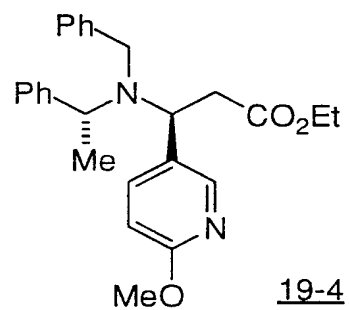
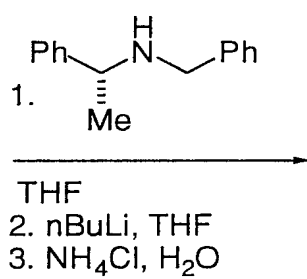
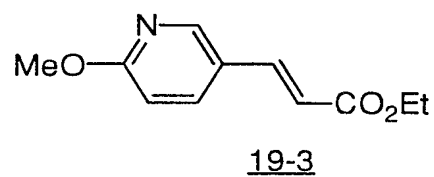
- A mixture of 5% Pd/BaSO<sub>4</sub> (0.025 g) and quinoline (0.30 mL) was stirred under a balloon of hydrogen for 30 minutes. 3-Amino-pent-4-ynoic acid ethyl ester (**18-1**) (for preparation, see J.A. Zablocki, et al., *J. Med. Chem.*, 1995, 38, 2378-2394) (1.77 g, 10.0 mmol) in EtOH (15 mL) was added and the solution stirred for an additional 2.5 hours. The solution was filtered through a pad of celite and concentrated in vacuo to provide 2.65 g of crude product **18-2**. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 8.40-7.60 (br s, 2H), 6.11-5.96 (m, 1H), 5.58-5.53 (d, 1H), 5.44-5.41 (d, 1H), 4.31-4.16 (m, 3H), 3.12-2.86 (m, 2H), 1.29-1.25 t, 3H).

20

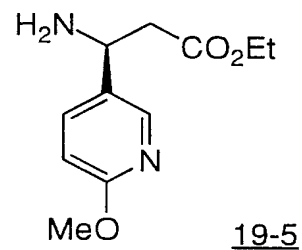
## SCHEME 19



$\text{Pd}(\text{OAc})_2$ ,  $\text{Et}_3\text{N}$ ,  
 tri-*o*-tolylphosphine  
 ethyl acrylate,  $\text{CH}_3\text{CN}$



$\text{Pd}(\text{OH})_2$ ,  $\text{H}_2$ ,  
 $\text{EtOH}$ ,  $\text{HOAc}$ ,  $\text{H}_2\text{O}$



5-Bromo-2-methoxypyridine (19-2)

To a solution of KOH (4.2 g, 0.075 mol) in water (750 mL) was added 2-methoxypyridine 19-1 (16.4 g, 0.15 mol) followed by a dropwise addition of bromine (24 g, 0.15 mol) in 1N aqueous KBr (750 mL) and the resulting solution was stirred at room temperature for 5 hr. Solid NaHCO<sub>3</sub> was added until basic and the solution was extracted with CHCl<sub>3</sub> (3x500 mL). The organic layer was washed with 10% NaHSO<sub>3</sub>, then brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent removed in vacuo. The resulting dark brown oil was predominantly the desired compound 19-2 and was used as such in the next step.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.91 (3H, s), 6.66 (1H, d), 7.62 (1H, dd), 8.20 (1H, d).

Ethyl 3-(6-methoxypyridin-3-yl)acrylate (19-3)

A solution of the 5-bromo-2-methoxypyridine 18-2 (74.3 g, 0.4 mol), ethyl acrylate (150 mL, 1.4 mol), triethylamine (150 mL, 1.08 mol), palladium acetate (10 g, 0.045 mol) and tri-*o*-tolylphosphine (20 g, 0.066 mol) in 100 mL acetonitrile was degassed with argon for 10 minutes. The mixture was heated at 90°C for 12 hr then the volatiles were removed in vacuo. Toluene (300 mL) was added and the mixture concentrated again. Diethyl ether (300 mL) was added and the mixture filtered through a pad of silica gel eluting with 800 mL of diethyl ether. After removal of the diethyl ether, the residue was chromatographed on silica gel eluting with EtOAc/hexane, 1:19 then 1:14 then 1:9, to give 19-3 as a yellow solid.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.34 (3H, t), 3.97 (3H, s), 4.26 (2H, q), 6.34 (1H, d), 6.76 (1H, d), 7.63 (1H, d), 7.77 (1H, dd), 8.27 (1H, d).

N-Benzyl-(R)-α-methylbenzyl-3(S)-(6-methoxypyridin-3-yl)-β-alanine ethyl ester (19-4)

To a solution of N-benzyl-(R)-α-methylbenzylamine (97.5 g, 462 mmol) in THF (750 mL) at 0°C was added n-butyllithium (2.5M in hexanes; 178.5 mL, 446 mmol). The dark violet solution was stirred at 0°C for 20 minutes, cooled to -78°C and the ester 19-3 (63.7 g, 308 mmol) in

THF (250 mL) was added over 60 minutes. The resulting solution was stirred at -78°C for 1 hr then cannulated into saturated NH<sub>4</sub>Cl and extracted with EtOAc, washed with water then brine, dried and concentrated *in vacuo* to give an oil. Column chromatography (silica gel; hexane/EtOAc, 9:1 then 4:1) gave 19-4 as an oil contaminated with N-benzyl-(R)- $\alpha$ -methylbenzylamine. This oil was taken up in 5% AcOH in water and extracted with diethyl ether (4x). The organic layers were dried over MgSO<sub>4</sub> and the solvent removed to give the title compound 19-4.

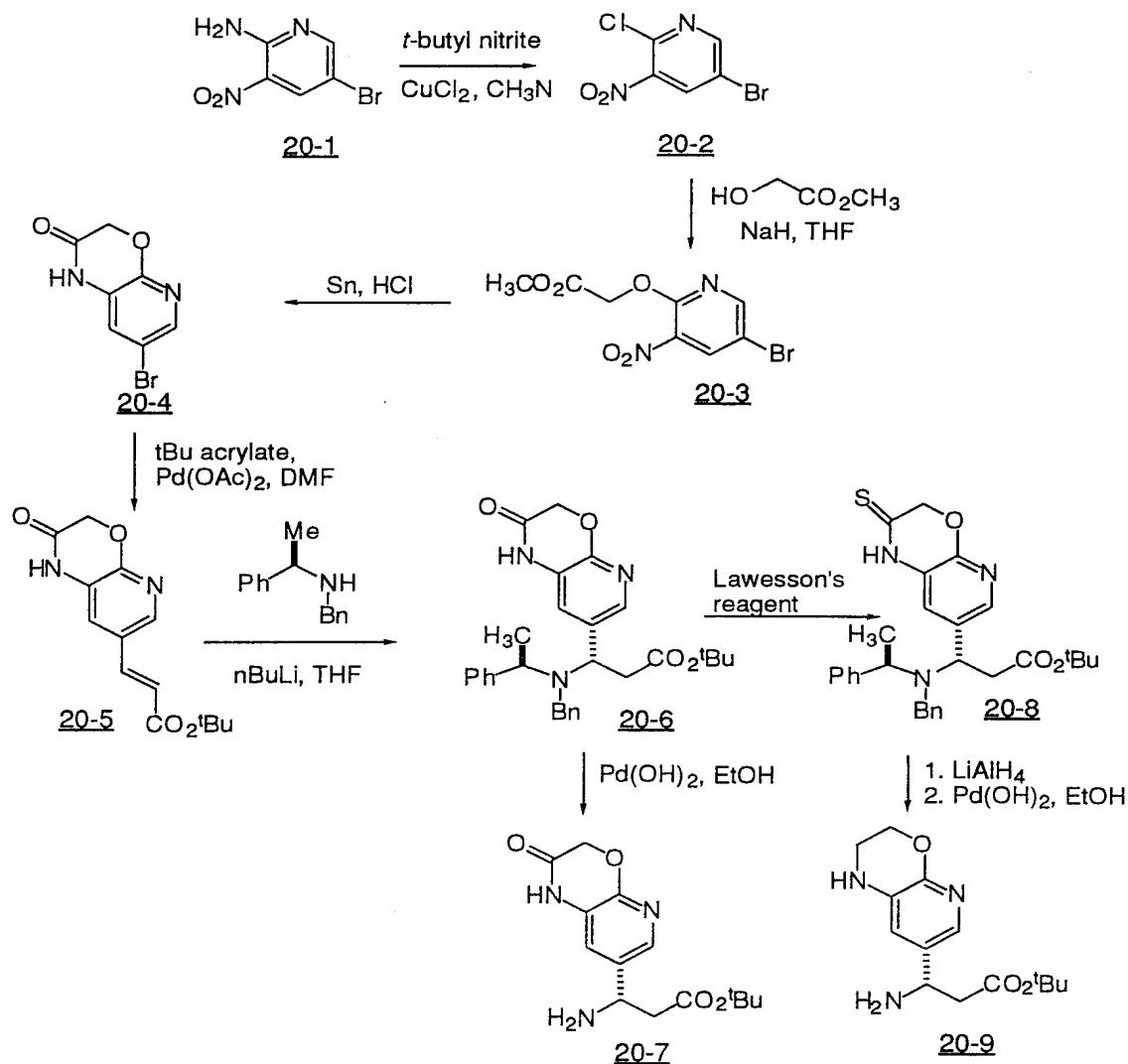
10 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.08 (3H, t), 1.27 (3H, d), 2.52 (1H, dd), 2.62 (1H, dd), 3.66 (1H, d), 3.70 (1H, d), 3.93 (3H, s), 3.95 (2H, m), 4.41 (1H, dd), 6.74 (1H, d), 7.15-7.45 (10H, m), 7.64 (1H, dd), 8.15 (1H, d).

3(S)-(2-methoxypyrid-5-yl)- $\beta$ -alanine ethyl ester (19-5)

15 To a degassed (argon) solution of the ester 19-4 (70 g) in EtOH (250 mL), HOAc (25 mL) and water (2 mL) was added 20% Pd(OH)<sub>2</sub> on carbon. The mixture was placed under hydrogen gas using a balloon and the resulting mixture was stirred for 24 hr. After filtration through celite (washing with EtOAc), the solvent was removed in vacuo to afford  
20 a waxy solid. This was dissolved in 200 mL water and extracted with diethyl ether (2x200 mL). The aqueous layer was then treated with solid K<sub>2</sub>CO<sub>3</sub> until fully saturated and extracted with 4x200 mL EtOAc. After drying over MgSO<sub>4</sub>, the solvent was removed in vacuo to give the title compound 19-5 as an oil which solidified in the freezer.

25 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.23 (3H, t), 2.61 (1H, dd), 2.68 (1H, dd), 3.92 (3H, s), 4.15 (2H, q), 4.41 (1H, dd), 6.93 (1H, d), 7.62 (1H, dd), 8.13 (1H, d).

Scheme 20

**3-Bromo-6-chloro-5-nitropyridine (20-2)**

- 5 A suspension of  $\text{CuCl}_2$  (3.33 g, 24.8 mmol) in anhydrous  $\text{CH}_3\text{CN}$  (200 mL) at  $65^\circ$  was treated with tert-butyl nitrite (3.13 mL, 26.3 mmol), followed by the dropwise addition of a solution of **20-1** in 60 ml of  $\text{CH}_3\text{CN}$ . The resulting mixture was stirred under an argon atmosphere at  $65^\circ$  for 2 h and concentrated at reduced pressure. The residue was partitioned between EtOAc (150 mL) and 3% HCl (60 ml),

and the organic layer washed successively with 3% HCl, water, and brine (60 mL), then dried, filtered and concentrated to afford a brown solid which was chromatographed on silica (25% EtOAc/Hexane) to afford 20-2 as a yellow crystalline solid.

5 TLC Rf = 0.60 (25% EtOAc/ Hexane)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.70 (d, J=2.4 Hz, 1H), 8.37 (d, J=2.4 Hz, 1H).

(3-Nitro-5-bromo-pyridin-2-yloxy)-acetic acid methyl ester (20-3)

Methyl glycolate (450 mg, 5.05 mmol) was added to a  
10 suspension of 60% NaH (131 mg, 55 mmol) in THF (20 mL) at 0°. The resulting solution was stirred under argon for 0.5 h, then treated with a solution of 20-2. After stirring at 0° for 0.5 h, the reaction was diluted with ethyl acetate, and washed with successively with sat. NaHCO<sub>3</sub>, water and brine (80 mL each), then dried, filtered and concentrated to  
15 afford 20-3 as a yellow solid.

TLC Rf = 0.70 (25% EtOAc/ Hexane)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.46 (d, J= 2.4 Hz, 1H), 8.37 (d, J= 2.4 Hz, 1H) 5.15 (s, 2H), 3.78 (s, 3H).

20 2-Oxo-2,3-dihydro-1H-4-oxa-1,5-diaza-7-bromo-naphthalene (20-4)

A mixture of 20-3 (1.5 g, 5.12 mmol) and powdered tin (1.37 g, 11.5 mmol) was treated with conc. HCl (10 mL). The mixture was heated to 80° for 2 h, then cooled and concentrated. The residue was partitioned between CHCl<sub>3</sub> and sat. NaHCO<sub>3</sub>, washed with brine, then  
25 dried, filtered and concentrated to afford a yellow solid. Chromatography on silica gel (50% hexane/EtOAc) gave 20-4 as a yellow solid.

TLC Rf = 0.65 (50% EtOAc/ Hexane)

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.81 (br,s, 1H), 7.88 (d, J=2.4 Hz, 1H),  
30 7.25 (d, J=2.4 Hz, 1H), 4.81 (s, 2H).

3-(2-Oxo-2,3-dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-acrylic acid tert-butyl ester (20-5)

A mixture of 20-4 (1.12 g, 4.89 mmol), (o-tol)<sub>3</sub>P (298 mg, 1.0 mmol), Pd(OAc)<sub>2</sub> (110 mg, 0.49 mmol), and triethylamine (0.86 mL, 5.87

mmol) in DMF (20 mL) was placed in a 100-mL flask. The mixture was degassed with argon, then tert-butyl acrylate (752 mg, 5.87 mmol) was added and the tube sealed and heated to 100° for 12 h. The reaction mixture was diluted with ethyl acetate, filtered and washed with  
5 NaHCO<sub>3</sub>, water, and brine, dried, filtered and concentrated. Chromatography on silica gel (25% hex/EtOAc) gave 20-5 as a yellow solid.

TLC R<sub>f</sub> = 0.60 (25% EtOAc/ Hexane)

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 10.91 (br,s, 1H), 8.15 (d, J=2.4 Hz, 1H),  
10 7.54 (d, J=16 Hz, 1 H), 7.42 (d, J= 2.4 Hz, 1H), 6.35 (d, J=16 Hz, 1 H), 4.84 (s, 2H), 1.48 (s, 9H).

3(S)-[Benzyl-(1(R)-phenylethyl)-amino]-3-(2-oxo-2,3-dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-propionic acid tert-butyl ester (20-6)

15 A solution of N-benzyl-α-(R)-methylbenzylamine (0.82 g, 3.87 mmol) in THF (25 mL) at 0°C was treated with n-BuLi (1.6 mL of a 2.5 M soln in hexanes). The resulting solution was stirred at 0°C for 30 min and then cooled to -78°C. A solution of acrylate 20-5 (0.485 g, 1.76 mmol) in THF (5 mL) was added. After stirring for 15 min at -78°C, satd aq  
20 NH<sub>4</sub>Cl soln (5 mL) was added and the cold bath removed. The mixture was warmed to room temperature, and extracted with Et<sub>2</sub>O (2 x 40 mL). The combined organic extracts were washed with brine (30 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography (40% ethyl acetate/hexanes) to give the β-  
25 aminoester 20-6 as a yellow oil.

TLC R<sub>f</sub> = 0.3 (40% ethyl acetate/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1H NMR 8.70 (br, s, 1H), 7.91 (d, J=1.8 Hz, 1H), 7.4-7.2 (10H), 7.12 (d, J=1.8 Hz, 1H), 4.80 (s, 2 H), 4.42 (m, 1H), 3.91 (q, J=6.7 Hz, 1 H), 3.69 (d, J=7.2 Hz, 1H, ), 3.62 (d, J =7.2 Hz, 1H, ), 2.46 (m,  
30 2H), 1.34 (d, J=7.0 Hz, 3H), 1.29 (s, 9H).

3(S)-Amino-3-(2-oxo-2,3-dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-propionic acid tert-butyl ester (20-7)

35 A mixture of the dibenzylamine 20-6 (0.22 g, 0.44 mmol) in EtOH/H<sub>2</sub>O/AcOH (26 mL/3 mL/1.0 mL) was degassed with argon and

treated with Pd(OH)<sub>2</sub> (100 mg). The mixture was placed under 1 atm of H<sub>2</sub>. After stirring for 18 h, the mixture was diluted with EtOAc and filtered through celite. The filtrate was concentrated and the residue purified by flash chromatography (20% 20:1:1 EtOH/NH<sub>4</sub>OH/H<sub>2</sub>O - 80%

5 EtOAc) to give the *tert*-butyl ester 20-7 as a white solid.

TLC R<sub>f</sub> = 0.5 (20% 20:1:1 EtOH/NH<sub>4</sub>OH/H<sub>2</sub>O - 80% EtOAc)

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.89 (d, J = 1.7 Hz, 1H), 7.31 (d, J = 1.7 Hz, 1H), 4.81 (s, 2H), 4.38 (m, 1H), 2.6, (m, 2H), 1.41 (s, 9H).

10 3(R)-[Benzyl-(1-phenylethyl)-amino]-3(S)-(2-thioxo-2,3-dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-propionic acid *tert*. butyl ester (20-8)

A solution of 20-6 (0.22 g, 0.44 mmol) in anhydrous THF was treated with Lawesson's reagent (0.098 g, 0.243 mmol) and stirred at room temperature for 1.5 h. Silica gel (500 mg) was added to the reaction mixture and the solvent was removed at reduced pressure and the product was eluted from silica using 25% EtOAc/hex to afford 20-8 as a yellow solid.

TLC R<sub>f</sub> = (40% EtOAc/hexane) 0.7

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 9.82 (br, s, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.4-

20 7.2 (11H), 5.08 (s, 2H), 4.42 (m, 1H), 3.91 (q, J = 6.7 Hz, 1H), 3.69 (d, J = 7.2 Hz, 1H), 3.62 (d, J = 7.2 Hz, 1H), 2.46 (m, 2H), 1.34 (d, J = 7.0 Hz, 3H), 1.29 (s, 9H).

25 3(S)-Amino-3-(2,3-dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-propionic acid *tert*. butyl ester (20-9)

A solution of 20-8 (1.0 g, 1.9 mmol) in anhydrous Et<sub>2</sub>O (10 mL) at 0° was treated dropwise with LiAlH<sub>4</sub> (2.09 ml of a 1.0 M solution in Et<sub>2</sub>O). The resulting solution was stirred at 0°C for 30 min and then quenched by the sequential addition of H<sub>2</sub>O (0.3 mL), 15 % NaOH (0.08 mL). Celite (1 g) was added and the mixture filtered through a Celite pad. The filtrate was evaporated and the residue was purified by flash chromatography (65% ethyl acetate/hexanes) to give the dibenzylamine intermediate as a yellow oil.

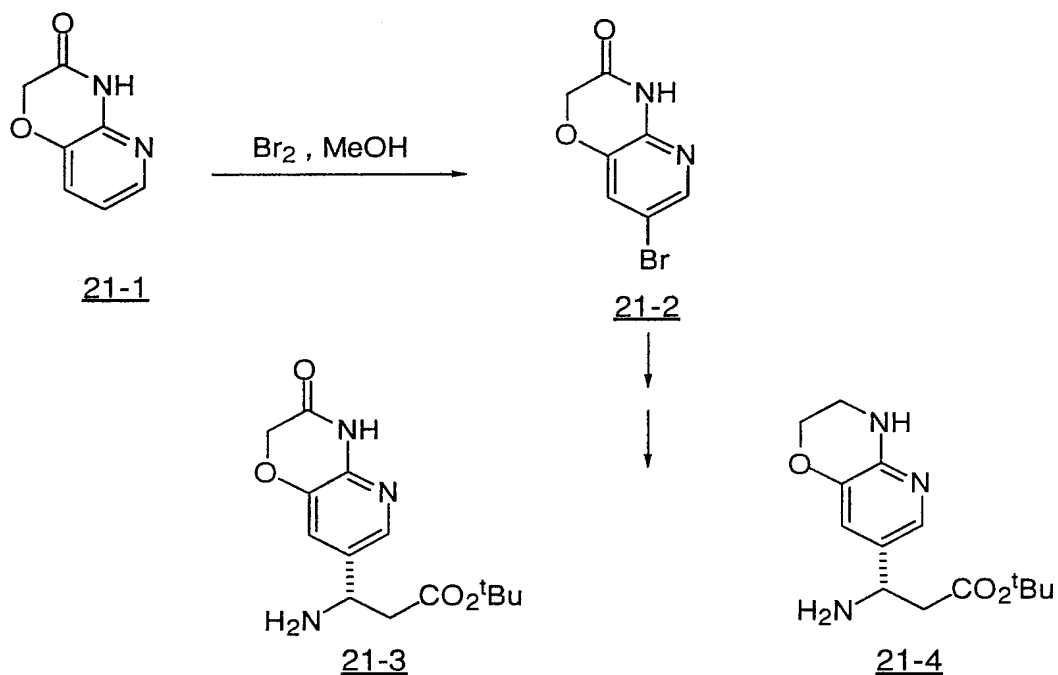
TLC R<sub>f</sub> = 0.4 (65% ethyl acetate/hexanes)



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1H NMR 7.61 (d,  $J=1.8$  Hz, 1H), 7.4-7.2 (10H), 6.87 (d,  $J=1.8$  Hz, 1H), 4.41 (m, 2H), 4.36 (m, 1H), 3.91 (q,  $J=6.7$  Hz, 1H), 3.8 (brs, 1H), 3.69 (m, 2H), 3.42 (m, 2H), 2.46 (m, 2H), 1.34 (d,  $J=7.0$  Hz, 3H), 1.29 (s, 9H).

- 5 This material was deprotected with  $\text{Pd}(\text{OH})_2$  to afford 20-9 as a white solid. TLC  $R_f = 0.5$  (20% 20:1:1 EtOH/ $\text{NH}_4\text{OH}$ / $\text{H}_2\text{O}$  - 80% EtOAc)  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.59 (d,  $J=1.7$  Hz, 1H), 6.92 (d,  $J=1.7$  Hz, 1H), 4.41 (m, 2H), 4.30 (m, 1H), , 3.41 (m, 2H), 2.6, (m, 2H), 1.41 (s, 9H).

Scheme 21



10

### 3-Oxo-3,4-dihydro-2H-1-oxa-4,5-diaza-7-bromo-naphthalene (21-2)

- A solution of 21-1 (4.8 g, 32 mmol) in MeOH (160 mL) at  $-15^\circ$  was treated dropwise with bromine (25.7 g, 161 mmol). After stirring at  $-15^\circ$  for 0.5 h, the mixture was warmed to ambient temperature and stirred overnight. The resulting white precipitate was filtered and washed with cold MeOH to afford 21-2 as a white solid.
- 15 TLC  $R_f = 0.65$  (50% EtOAc/ Hexane)

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  11.2 (br, s, 1H), 8.05 (d,  $J$  = 2.4 Hz, 1H), 7.66 (d,  $J$  = 2.4 Hz, 1H), 4.76 (s, 2H).

5 3(S)-Amino-3-(3-oxo-3,4-dihydro-2H-1-oxa-4,5-diaza-naphthalen-7-yl)-propionic acid *tert*-butyl ester (21-3)

Bromide 21-2 was converted to amino ester 21-3 as illustrated in Scheme 20.

TLC  $R_f$  = 0.5 (12% 20:1:1 EtOH/ $\text{NH}_4\text{OH}$ / $\text{H}_2\text{O}$  - 88% EtOAc)

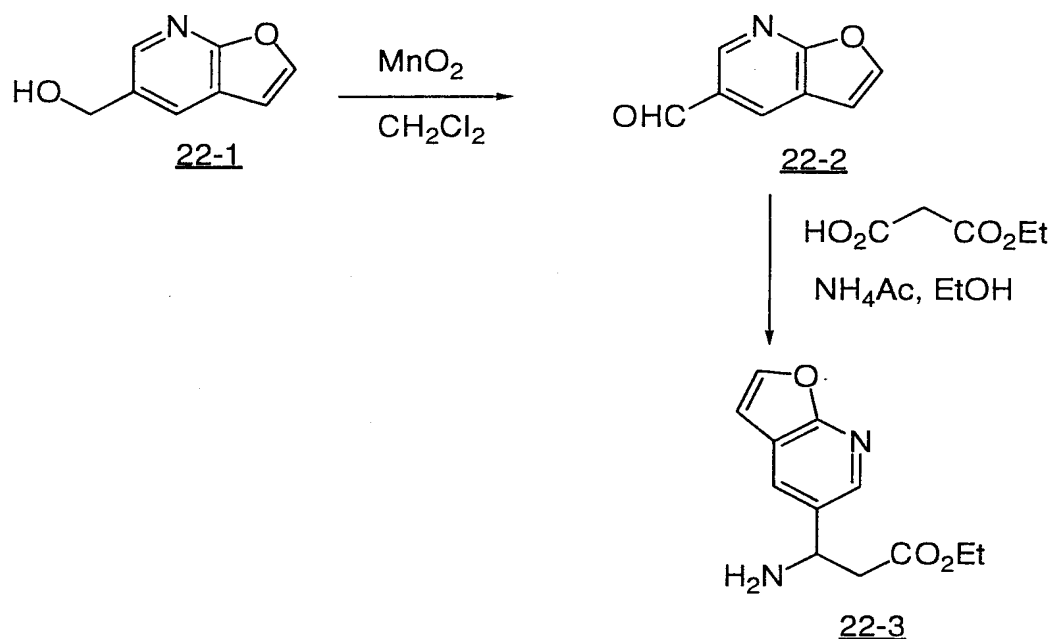
10  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.04 (d,  $J$  = 1.7 Hz, 1H), 7.34 (d,  $J$  = 1.7 Hz, 1H), 4.76 (s, 2H), 4.38 (m, 1H), 2.6, (m, 2H), 1.41 (s, 9H).

3(S)-Amino-3-(3-oxo-3,4-dihydro-2H-1-oxa-4,5-diaza-naphthalen-7-yl)-propionic acid *tert*-butyl ester (21-4)

15 Bromide 21-2 was converted to amino ester 21-4 as illustrated in Scheme 20.

TLC  $R_f$  = 0.5 (20% 20:1:1 EtOH/ $\text{NH}_4\text{OH}$ / $\text{H}_2\text{O}$  - 80% EtOAc)

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.04 (d,  $J$  = 1.7 Hz, 1H), 7.34 (d,  $J$  = 1.7 Hz, 1H), 4.76 (s, 2H), 4.38 (m, 1H), 2.6, (m, 2H), 1.41 (s, 9H).

Scheme 22Furo-[2,3-b]pyridine-5-carboxaldehyde (22-2)

A solution of alcohol 22-1 (M. Bhupathy, et al., J. Heterocycl. Chem. 1995, 32, 1283-1287) was treated with excess  $\text{MnO}_2$  (10 eq) and the mixture stirred at room temperature for 16 h, then filtered through Celite and evaporated to afford 22-2 as a white solid.

TLC  $R_f$  = 0.40 (25% EtOAc/Hex)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.22 (s, 1H), 9.05 (d,  $J$  = 1.8 Hz, 1H), 8.27 (d,  $J$  = 1.7 Hz, 1H) 8.08 (d,  $J$  = 1.8 Hz, 1H), 7.10 (d,  $J$  = 1.7 Hz, 1H).

3-Amino-3-(furo[2,3-b]pyridin-5-yl)-propionic acid ethyl ester (22-3)

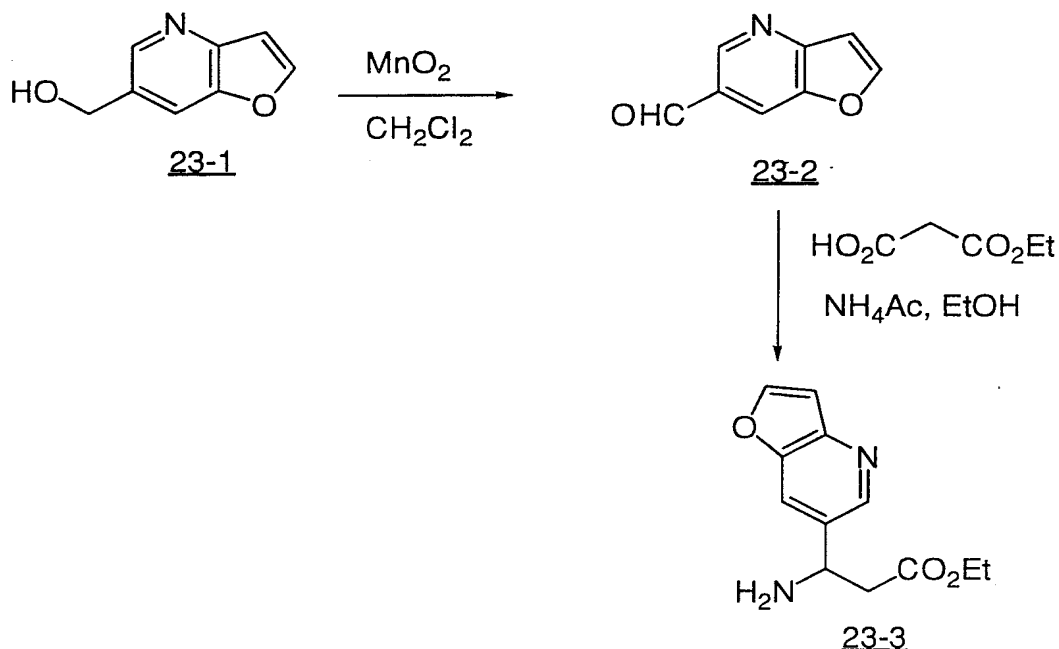
A solution containing aldehyde 22-2 (1.5 g, 10 mmol), ethyl hydrogen malonate (1.6 g, 20 mmol), and ammonium acetate (3.8 g, 50 mmol) in anhydrous ethanol (125 mL) was heated at reflux for 8 h. After cooling to room temperature, the solvent was evaporated and the residue partitioned between sat. sodium bicarbonate and EtOAc, the organic layer removed, dried, and concentrated. Chromatography of the residue afforded the amino ester 22-3 as a waxy solid.

TLC  $R_f$  = 0.5 (20% 20:1:1 EtOH/NH<sub>4</sub>OH/H<sub>2</sub>O - 80% EtOAc)

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  8.34 (d, J=1.7 Hz, 1H), 8.04 (d, J=1.7 Hz, 1H), 7.72 (d, J= 1.7 Hz, 1H), 6.78 (d, J = 1.7 Hz, 1H), 4.62 (m, 1H), 4.13 (q, J=7.5 Hz, 2H), 3.20 (br, s, 2H), 2.76 (m, 2H), 1.23 (t, J= 7.5 Hz, 3H).

5

### Scheme 23



### Furo[3,2-b]pyridine-5-carboxaldehyde (23-2)

A solution of alcohol 23-1 (J.M. Hoffman, Jr., US Patent No. 4,808,595) was treated with excess MnO<sub>2</sub> (10 eq) and the mixture stirred at room temperature for 16 h, then filtered through Celite and evaporated to afford 23-2 as a white solid.

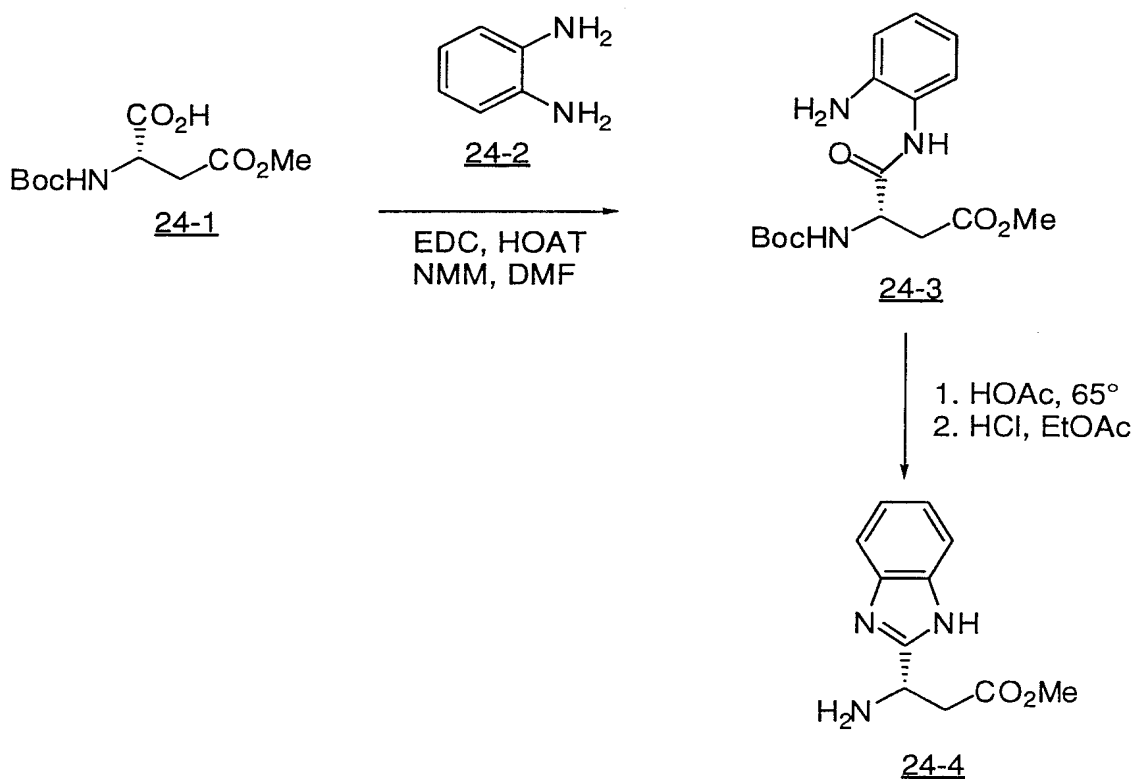
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  10.18 (s, 1H), 8.92 (d, J= 1.8 Hz, 1H), 8.17 (d, J=1.7 Hz, 1H) 7.89 (d, J=1.8 Hz, 1H), 7.10 (d, J=1.7 Hz, 1H).

15

### 3-Amino-3-(furo[3,2-b]pyridin-5-yl)-propionic acid ethyl ester (23-3)

A solution containing aldehyde 23-2 (1.5 g, 10 mmol), ethyl hydrogen malonate (1.6 g, 20 mmol), and ammonium acetate (3.8 g, 50

mmol) in anhydrous ethanol (125 mL) was heated at reflux for 8 h. After cooling to room temperature, the solvent was evaporated and the residue partitioned between sat. sodium bicarbonate and EtOAc, the organic layer removed, dried, and concentrated. Chromatography of the residue  
5 afforded the amino ester 23-3 as a waxy solid.  
TLC  $R_f$  = 0.5 (20% 20:1:1 EtOH/NH<sub>4</sub>OH/H<sub>2</sub>O - 80% EtOAc)  
<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  8.58 (d,  $J$ =1.7 Hz, 1H), 7.89 (d,  $J$ =1.7 Hz, 1H), 7.85 (d,  $J$ =1.7 Hz, 1H), 6.98 (d,  $J$ =1.7 Hz, 1H), 4.62 (t,  $J$ =7.2 Hz, 1H),  
4.09 (q,  $J$ =7.5 Hz, 2H), 2.76 (m, 2H), 2.20 (br, s, 2H), 1.21 (t,  $J$ =7.5 Hz, 3H).  
10

Scheme 24

N-(S)-(2-Amino-phenyl)-3-tert-butoxycarbonylamino-succinamic acid methyl ester (24-3)

5 A mixture of Boc-L-aspartic acid- $\beta$ -methyl ester 24-1 (5.0g, 20.2 mmol), o-phenylenediamine 24-2 (2.2 g, 20.2 mmol), EDC (3.9 g, 20.2 mmol), HOAT (0.28 g, 2.02 mmol), and NMM (6.7 mL, 60.7 mmol) in DMF (50 mL) was stirred for 18 h at ambient temperature. The solution was diluted with EtOAc (250 mL) and washed with sat. sodium bicarbonate, water, and brine (50 mL each), then dried and evaporated to afford 24-3 as a yellow solid.

10 TLC R<sub>f</sub> = 0.50 (95% CHCl<sub>3</sub>/5% isopropanol)

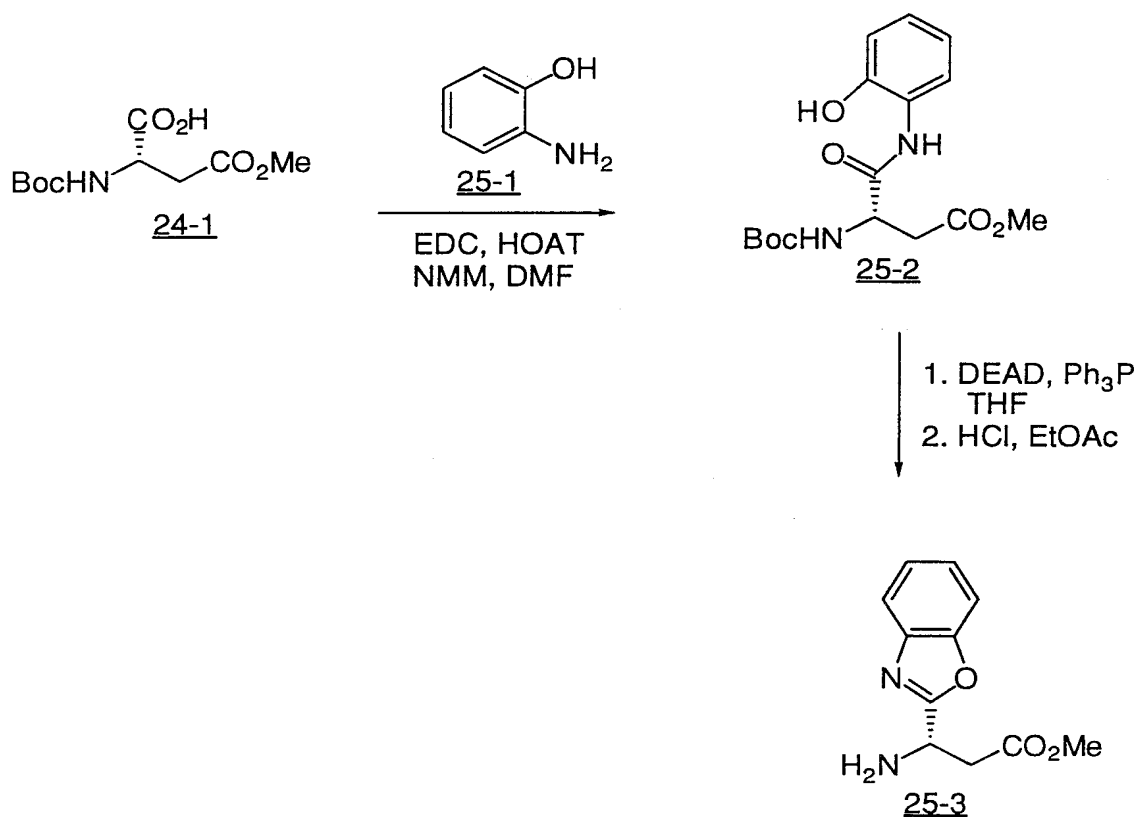
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.10 (br,s, 1H), 7.23 (d, J= 7.8 Hz, 1H), 7.08 (t, J=7.8 Hz, 1H), 6.78 (m, 1H), 5.8 (br d, 1H), 4.65 (m, 1 H), 3.76 (s, 3H), 3.15 (dd, J=4.6, 16 Hz, 1H), 2.90 (dd, J= 5.1, 16 Hz, 1H), 1.48 (s, 9H).

15 3(S)-Amino-3-Benzimidazol-2-yl-propionic acid methyl ester (24-4)

Ester 24-3 (1.0 g, 3 mmol) was dissolved in acetic acid (50 mL) and heated to 65° for 2 h. The solvent was removed to afford the Boc-protected intermediate as a white solid. The crude material (920 mg, 2.43 mmol) was dissolved in EtOAc, cooled to 0°, and treated with HCl gas to give 24-4 as a tan solid.

20 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.80 (m, 2H), 7.35 (m, 2H), 5.98 (m, 1H), 3.80 (m, 2H), 3.76 (s, 3H).

Scheme 25



N-(S)-(2-Hydroxy-phenyl)-3-tert-butoxycarbonylamino-succinamic acid methyl ester (25-2)

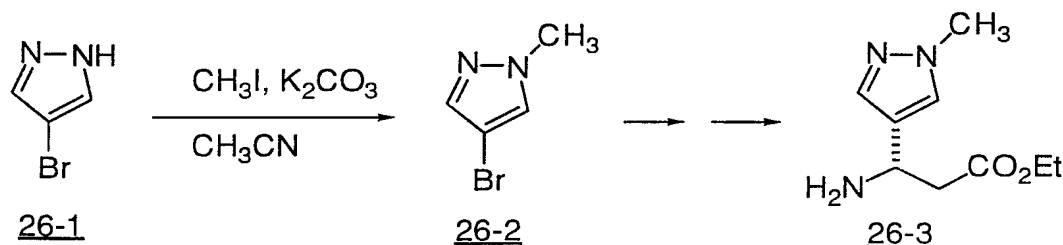
- A mixture of Boc-L-aspartic acid-β-methyl ester (24-1) (5.0g, 20.2 mmol), 2-amino phenol (25-1) (2.2 g, 20.2 mmol), EDC (3.9 g, 20.2 mmol), HOAT (0.28 g, 2.02 mmol), and NMM (6.7 mL, 60.7 mmol) in DMF (50 mL) was stirred for 18 h at ambient temperature. The solution was diluted with EtOAc (250 mL) and washed with sat. sodium bicarbonate, water, and brine (50 mL each), then dried, and evaporated and chromatographed on silica (EtOAc) to afford 25-2 as a white solid. TLC R<sub>f</sub> = 0.55 (EtOAc)
- <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.23 (d, J= 7.8 Hz, 1H), 6.89 (t, J=7.8 Hz, 1H), 6.78 (m, 1H), 5.68 (br d, 1H), 4.65 (m, 1 H), 3.76 (s, 3H), 3.15 (dd, J=4.6, 16 Hz, 1H), 2.90 (dd, J= 5.1, 16 Hz, 1H), 1.48 (s, 9H).

15

3(S)-Amino-3-Benzoxazol-2-yl-propionic acid methyl ester (25-3)

Ester 25-2 (2.0 g, 6.0 mmol) was dissolved in anhydrous THF (150 mL) along with Ph<sub>3</sub>P (1.58 g, 6.0 mmol). The resulting solution was cooled to 0°, and a solution of diethyl azodicarboxylate (1.53 g, 6.2 mmol) in THF (25 mL) was added dropwise. The cooling bath was removed and the solution stirred overnight at ambient temperature. The solution was concentrated and the residue chromatographed (75% EtOAc/Hexane) to afford the Boc-protected ester as a colorless glass. The crude material (1.8 g, 5.0 mmol) was dissolved in EtOAc, cooled to 0° and treated with HCl gas to give 25-3 as a tan solid.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.81 (m, 2H), 7.40 (m, 2H), 5.05 (t, J = 7.4 Hz, 1H), 3.72 (s, 3H), 3.30 (m, 2H).

SCHEME 261-Methyl-4-bromopyrazole (26-2)

Methyl iodide (8.47 mL, 136 mmol) was added to a mixture of 4-bromopyrazole 26-1 (10 g, 38 mmol), and K<sub>2</sub>CO<sub>3</sub> (18.9 g, 136 mmol) in CH<sub>3</sub>CN (150 mL) and the mixture stirred at room temperature for 16 h, then filtered and evaporated to yield 26-2 as a yellow oil.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.44 (s, 1H), 7.38 (s, 1H), 3.90 (s, 3H).

3 (S)-Amino-3-(1-methyl-1H-pyrazol-4-yl)-propionic acid ethyl ester (26-3)

The bromide 26-2 was converted to the amino ester 26-3 following the procedure depicted in Scheme 19.

<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.81 (s, 1H), 7.58 (s, 1H), 4.80 (m, 1H), 4.05 (q, J = 7.0 Hz, 2 H), 3.89 (s, 3H), 3.00 (m, 2 H), 1.24 (t, J = 7.0 Hz, 3 H).



Additional examples of the present invention are listed below and can be prepared by the method shown in Scheme 2 using in place of 1-4 the various 3-substituted  $\beta$ -alanine derivatives prepared according to the procedures depicted in Schemes 9-26 above. These  
5 examples can be prepared in high optical purity substituting intermediate 7-5 or its enantiomer for intermediate 2-5.

3(S)-(6-Ethoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;  
10

3(S)-(6-Amino-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3(S)-(4-Methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-3-(2-oxo-3-[3-  
15 (5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-  
propionic acid;

3-(6-Methylamino-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;  
20

3(S)-(2-Fluoro-biphenyl-4-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3(S)-(2-Oxo-2,3-dihydro-benzoxazol-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-  
25 [1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3(S)-(4-Ethoxy-3-fluorophenyl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

30 3(S)-(5-Ethoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3(S)-(5-Methoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-  
[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;  
35

3(S)-(Ethynyl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

5 3(S)-(6-Methoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

10 3(S)-(2-Oxo-2,3-dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3(S)-(2,3-Dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

15 3(S)-(2-Oxo-3,4-dihydro-2H-1-oxa-4,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

20 3(S)-(3,4-Dihydro-2H-1-oxa-4,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

25 3-(Furo-[2,3-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3-(2,3-Dihydrofuro[2,3-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

30 3-(Furo-[3,2-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3-(2,3-Dihydrofuro[3,2-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3(S)-(Benzimidazol-2-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

5 3(S)-(1H-Imidazo[4,5-c]pyridin-2-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

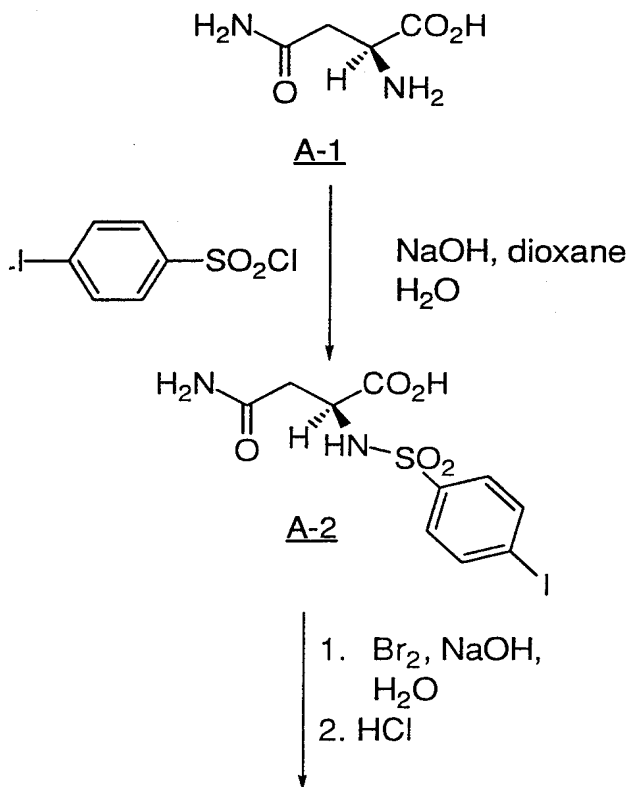
3(S)-(Benzoxazol-2-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

10 3(S)-(1-Methyl-1H-pyrazol-4-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid; and

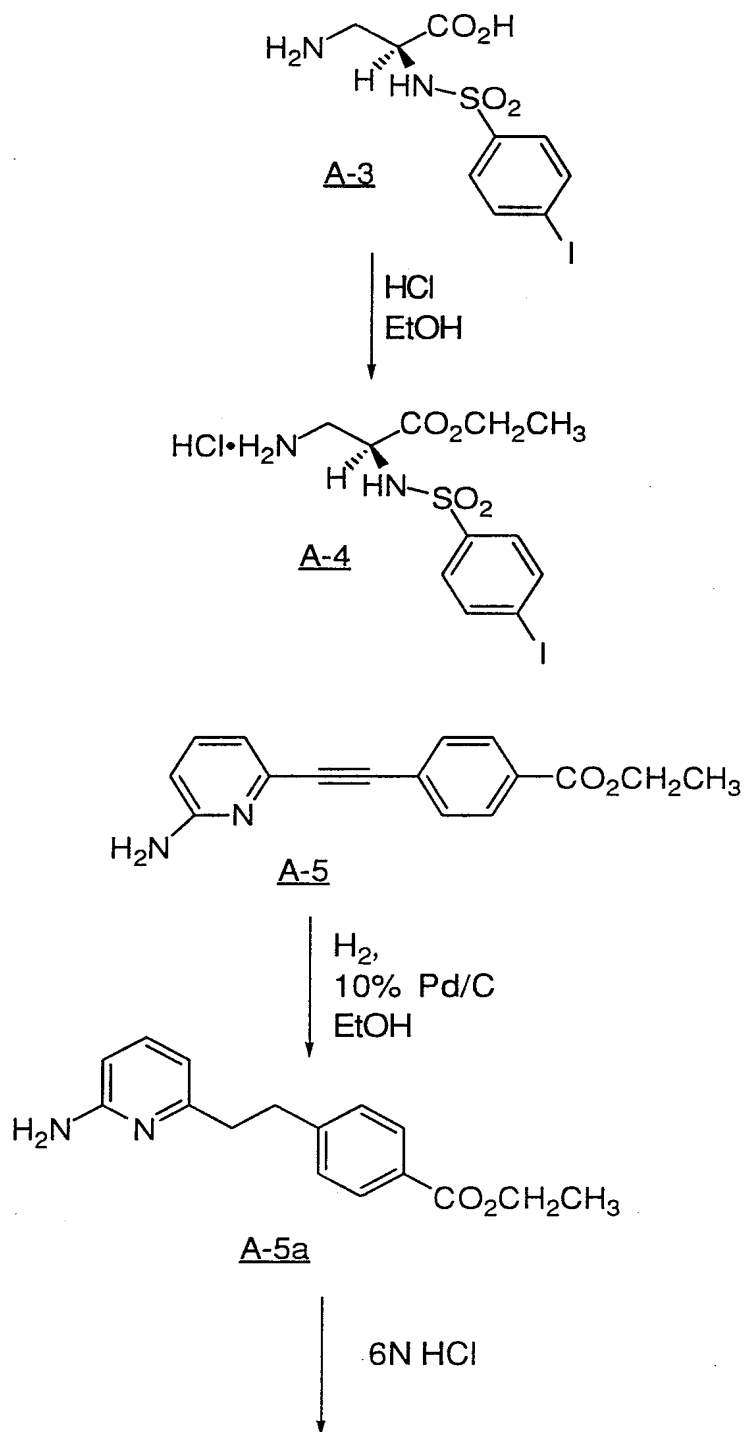
3(S)-(2-Oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-pent-4-enoic acid.

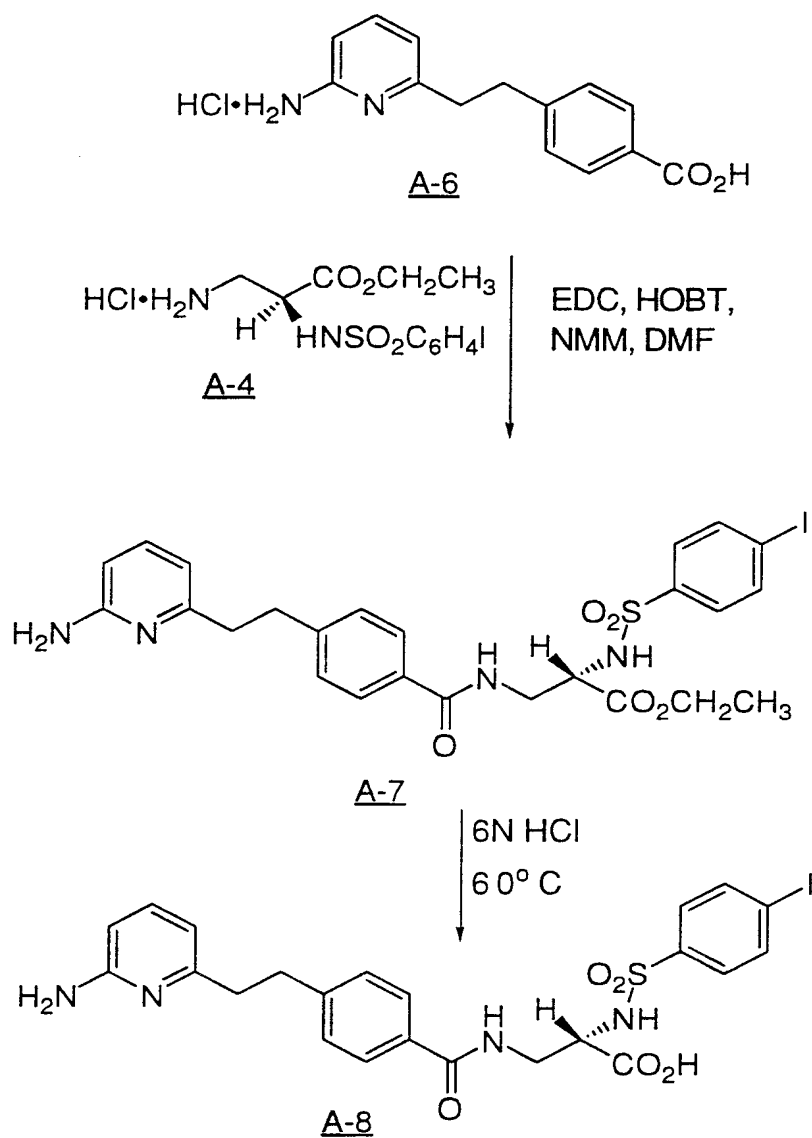
SCHEME A

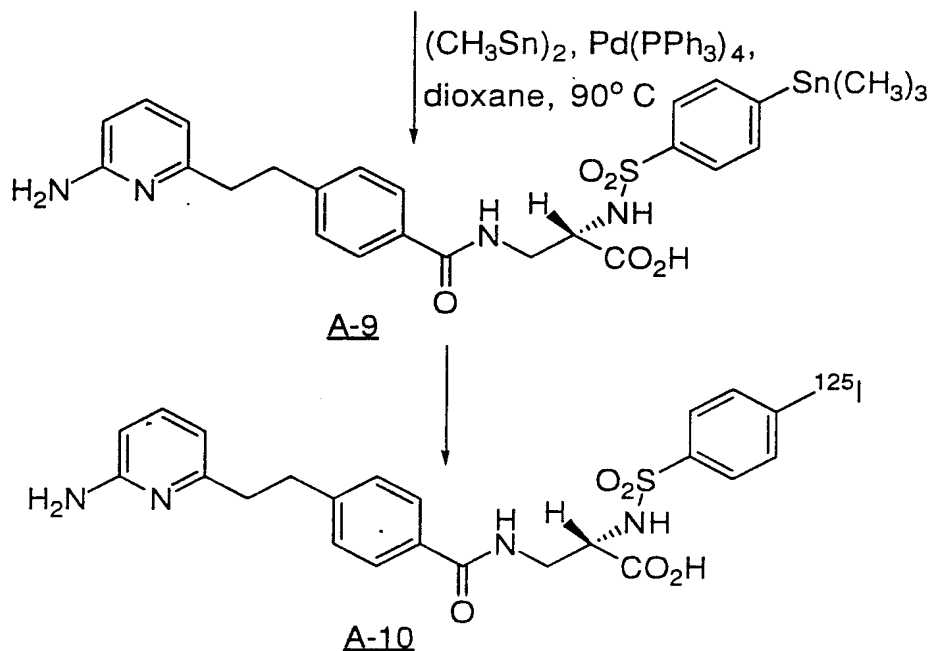
5

SYNTHESIS OF RADIOLIGAND FOR SPA ASSAY

10

SCHEME A (CONTINUED)

SCHEME A (CONTINUED)



N-(4-Iodo-phenylsulfonylamino)-L-asparagine (A-2)

- 5 To a stirred solution of acid A-1 (4.39 g, 33.2 mmol), NaOH (1.49 g, 37.2 mmol), dioxane (30 ml) and H<sub>2</sub>O (30 ml) at 0°C was added pipsyl chloride (10.34 g, 34.2 mmol). After ~5 minutes, NaOH (1.49, 37.2 mmol), dissolved in 15 ml H<sub>2</sub>O, was added followed by the removal of the cooling bath. After 2.0 h, the reaction mixture was concentrated. The residue was dissolved in H<sub>2</sub>O (300 ml) and then washed with EtOAc.
- 10 The aqueous portion was cooled to 0°C and then acidified with concentrated HCl. The solid was collected and then washed with Et<sub>2</sub>O to provide acid A-2 as a white solid.
- <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O) δ 7.86 (d, 2H, J=8Hz), 7.48 (d, 2H, J=8Hz) 3.70 (m, 1H), 2.39 (m, 2H).

15

2(S)-(4-Iodo-phenylsulfonylamino)-β-alanine (A-3)

To a stirred solution of NaOH (7.14 g, 181.8 mmol) and H<sub>2</sub>O (40 ml) at 0°C was added Br<sub>2</sub> (1.30 ml, 24.9 mmol) dropwise over a ten

minute period. After ~5 minutes, acid A-2 (9.9 g, 24.9 mmol), NaOH (2.00 g, 49.8 mmol) and H<sub>2</sub>O (35 ml) were combined, cooled to 0°C and then added in a single portion to the reaction. After stirring for 20 minutes at 0°C, the reaction was heated to 90°C for 30 minutes and then recooled to 0°C. The pH was adjusted to ~7 by dropwise addition of concentrated HCl. The solid was collected, washed with EtOAc, and then dried *in vacuo* to provide acid A-3 as a white solid.  
5 <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O) δ 8.02 (d, 2H, J=8Hz), 7.63 (d, 2H, J=8Hz), 4.36 (m, 1H), 3.51 (dd, 1H, J=5Hz, 13Hz) 3.21 (m, 1H).

10

Ethyl 2(S)-(4-iodo-phenylsulfonylamino)-β-alanine-hydrochloride (A-4)

HCl gas was rapidly bubbled through a suspension of acid A-3 (4.0 g, 10.81 mmol) in EtOH (50 ml) at 0°C for 10 minutes. The cooling bath was removed and the reaction was heated to 60°C. After 18 h, the reaction was concentrated to provide ester A-4 as a white solid.  
15 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.98 (d, 2H, J=8Hz), 7.63 (d, 2H, J=8Hz), 4.25 (q, 1H, J=5Hz), 3.92 (m, 2H), 3.33 (m, 1H), 3.06 (m, 1H), 1.01 (t, 3H, J=7Hz).

20 Ethyl 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoate (A-5a)

A mixture of ester A-5 (700 mg, 2.63 mmol), (for preparation, see: Scheme 29 of PCT International Application Publication No. WO 95/32710, published December 7, 1995) 10% Pd/C (350 mg) and EtOH were stirred under 1 atm H<sub>2</sub>. After 20 h, the reaction was  
25 filtered through a celite pad and then concentrated to provide ester A-5a as a brown oil.

TLC R<sub>f</sub> = 0.23 (silica, 40% EtOAc/hexanes)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.95 (d, 2H, J=8Hz), 7.26 (m, 3H), 6.43 (d, 1H, J=7Hz), 6.35 (d, 1H, J=8Hz), 4.37 (m, 4H), 3.05 (m, 2H), 2.91 (m, 2H),  
30 1.39 (t, 3H, J=7Hz).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoic acid hydrochloride (A-6)

A suspension of ester A-5a (625 mg, 2.31 mmol) in 6N HCl (12 ml) was heated to 60°C. After ~20 h, the reaction was concentrated to  
35 give acid A-6 as a tan solid.



<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.96 (d, 2H, J=8Hz), 7.80 (m, 1H), 7.33 (d, 2H, J=8Hz), 6.84 (d, 1H, J=9Hz), 6.69 (d, 1H, J=7Hz), 3.09 (m, 4H).

5 Ethyl 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-iodo-phenylsulfonylamino)-β-alanine (A-7)

A solution of acid 15-6 (400 mg, 1.43 mmol), amine A-4 (686 mg, 1.57 mmol), EDC (358 mg, 1.86 mmol), HOBT (252 mg, 1.86 mmol), NMM (632 μl, 5.72 mmol) in DMF (10 ml) was stirred for ~20 h. The reaction was diluted with EtOAc and then washed with sat. NaHCO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (silica, EtOAc then 5% isopropanol/EtOAc) provided amide A-7 as a white solid.  
TLC R<sub>f</sub> = 0.4 (silica, 10% isopropanol/EtOAc)  
<sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.79 (d, 2H, J=9Hz) 7.61 (d, 2H, J=8Hz), 7.52 (d, 2H, J=9Hz), 7.29 (m, 1H), 7.27 (d, 2H, J=8Hz), 4.20 (m, 1H), 3.95 (q, 2H, J=7Hz), 3.66 (dd, 1H, J=6Hz, 14Hz), 3.49 (dd, 1H, J=8Hz, 13Hz), 3.01 (m, 2H), 2.86 (m, 2H), 1.08 (t, 3H, J=7Hz).

20 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-iodophenyl-sulfonylamino)-β-alanine (A-8)

A solution of ester A-7 (200 mg, 0.3213 mmol) and 6N HCl (30 ml) was heated to 60°C. After ~20 h, the reaction mixture was concentrated. Flash chromatography (silica, 20:20:1:1 EtOAc/EtOH/NH<sub>4</sub>OH/H<sub>2</sub>O) provided acid A-8 as a white solid.  
TLC R<sub>f</sub> = 0.45 (silica, 20:20:1:1 EtOAc/EtOH/NH<sub>4</sub>OH/H<sub>2</sub>O)  
<sup>1</sup>H NMR (400 MHz, DMSO) δ 8.40 (m, 1H), 8.14 (Bs, 1H), 7.81 (d, 2H, J=8Hz), 7.62 (d, 2H, J=8Hz), 7.48 (d, 2H, J=8Hz), 7.27 (m, 3H), 6.34 (d, 1H, J=7Hz), 6.25 (d, 1H, J=8Hz), 5.85 (bs, 2H), 3.89 (bs, 1H), 3.35 (m, 2H), 2.97 (m, 2H), 2.79 (m, 2H).

30 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-trimethylstannyl-phenylsulfonylamino)-β-alanine (A-9)

A solution of iodide A-8 (70 mg, 0.1178 mmol), [(CH<sub>3</sub>)<sub>3</sub>Sn]<sub>2</sub> (49 μl, 0.2356 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mg) and dioxane (7 ml) was heated to

90°C. After 2 h, the reaction was concentrated and then purified by preparative HPLC (Delta-Pak C<sub>18</sub> 15 µM 100Å, 40 x 100 mm; 95:5 then 5:95 H<sub>2</sub>O/CH<sub>3</sub>CN) to provide the trifluoroacetate salt. The salt was suspended in H<sub>2</sub>O (10 ml), treated with NH<sub>4</sub>OH (5 drops) and then lyophilized to provide amide A-9 as a white solid.

<sup>1</sup>H NMR (400 MHz, DMSO) δ 8.40 (m, 1H), 8.18 (d, 1H, J=8Hz), 7.67 (m, 5H), 7.56 (d, 2H, J=8Hz), 7.29 (d, 2H, J=8Hz), 6.95-7.52 (m, 2H), 6.45 (bs, 2H), 4.00 (m, 1H), 3.50 (m, 1H), 3.33 (m, 1H), 2.97 (m, 2H), 2.86 (m, 2H).

10 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-4-<sup>125</sup>Iodo-phenylsulfonfylamino-β-alanine (A-10)

An iodobead (Pierce) was added to a shipping vial of 5 mCi of Na<sup>125</sup>I (Amersham, IMS30) and stirred for five minutes at room temperature. A solution of 0.1 mg of A-9 in 0.05 mL of 10% H<sub>2</sub>SO<sub>4</sub>/MeOH was made and immediately added to the Na<sup>125</sup>I/iodobead vial. After stirring for three minutes at room temperature, approximately 0.04-0.05 mL of NH<sub>4</sub>OH was added so the reaction mixture was at pH 6-7. The entire reaction mixture was injected onto the HPLC for purification [Vydac peptide-protein C-18 column, 4.6 x 250 mm, linear gradient of 10% acetonitrile (0.1% (TFA):H<sub>2</sub>O (0.1% TFA) to 90% acetonitrile (0.1% TFA):H<sub>2</sub>O (0.1% TFA) over 30 minutes, 1 mL/min]. The retention time of A-10 is 17 minutes under these conditions. Fractions containing the majority of the radioactivity were pooled, lyophilized and diluted with ethanol to give approximately 1 mCi of A-10, which coeluted on HPLC analysis with an authentic sample of A-8.

Instrumentation: Analytical and preparative HPLC was carried out using a Waters 600E Powerline Multi Solvent Delivery System with 0.1 mL heads with a Rheodyne 7125 injector and a Waters 990 Photodiode Array Detector with a Gilson FC203 Microfraction collector. For analytical and preparative HPLC, a Vydac peptide-protein C-18 column, 4.6 x 250 mm was used with a C-18 Brownlee modular guard column. The acetonitrile used for the HPLC analyses was Fisher Optima grade. The HPLC radiodetector used was a Beckman 170 Radioisotope detector. A Vydac C-18 protein and peptide column, 3.9 x

250 mm was used for analytical and preparative HPLC. Solutions of radioactivity were concentrated using a Speedvac vacuum centrifuge. Calibration curves and chemical concentrations were determined using a Hewlett Packard Model 8452A UV/Vis Diode Array Spectrophotometer.  
5 Sample radioactivities were determined in a Packard A5530 gamma counter.

The test procedures employed to measure  $\alpha\beta 3$  and  $\alpha\beta 5$  binding and the bone resorption inhibiting activity of the compounds of the present invention are described below.

10

#### BONE RESORPTION-PIT ASSAY

When osteoclasts engage in bone resorption, they can cause the formation of pits in the surface of bone that they are acting upon. Therefore, when testing compounds for their ability to inhibit  
15 osteoclasts, it is useful to measure the ability of osteoclasts to excavate these resorption pits when the inhibiting compound is present.

Consecutive 200 micron thick cross sections from a 6 mm cylinder of bovine femur diaphysis are cut with a low speed diamond saw (Isomet, Beuler, Ltd., Lake Bluff, IL). Bone slices are pooled, placed  
20 in a 10% ethanol solution and refrigerated until further use.

Prior to experimentation, bovine bone slices are ultrasonicated twice, 20 minutes each in H<sub>2</sub>O. Cleaned slices are placed in 96 well plates such that two control lanes and one lane for each drug dosage are available. Each lane represents either triplicate or  
25 quadruplicate cultures. The bone slices in 96 well plates are sterilized by UV irradiation. Prior to incubation with osteoclasts, the bone slices are hydrated by the addition of 0.1 ml  $\alpha$ MEM, pH 6.9 containing 5% fetal bovine serum and 1% penicillin/streptomycin.

Long bones from 7-14 day old rabbits (New Zealand White  
30 Hare) are dissected, cleaned of soft tissue and placed in  $\alpha$ MEM containing 20 mM HEPES. The bones are minced using scissors until the pieces are <1 mm and transferred to a 50 ml tube in a volume of 25 ml. The tube is rocked gently by hand for 60 cycles, the tissue is sedimented for 1 min., and the supernatant is removed. Another 25 ml  
35 of medium is added to the tissue and rocked again. The second

supernatant is combined with the first. The number of cells is counted excluding erythrocytes (typically  $\sim 2 \times 10^7$  cells/ml). A cell suspension consisting of  $5 \times 10^6$ /ml in  $\alpha$ MEM containing 5% fetal bovine serum, 10 nM  $1,25(\text{OH})_2\text{D}_3$ , and pencillin-streptomycin is prepared. 200 ml  
5 aliquots are added to bovine bone slices (200 mm x 6 mm) and incubated for 2 hrs. at  $37^\circ\text{C}$  in a humidified 5%  $\text{CO}_2$  atmosphere. The medium is removed gently with a micropipettor and fresh medium containing test compounds is added. The cultures are incubated for 48 hrs., and assayed for c-telopeptide (fragments of the  $\alpha 1$  chain of type I collagen) by  
10 Crosslaps for culture media (Herlev, Denmark).

Bovine bone slices are exposed to osteoclasts for 20-24 hrs and are processed for staining. Tissue culture media is removed from each bone slice. Each well is washed with 200 ml of  $\text{H}_2\text{O}$ , and the bone slices are then fixed for 20 minutes in 2.5% glutaraldehyde, 0.1 M  
15 cacodylate, pH 7.4. After fixation, any remaining cellular debris is removed by 2 min. ultrasonication in the presence of 0.25 M  $\text{NH}_4\text{OH}$  followed by 2 X 15 min ultrasonication in  $\text{H}_2\text{O}$ . The bone slices are immediately stained for 6-8 min with filtered 1% toluidine blue and 1% borax.

20 After the bone slices have dried, resorption pits are counted in test and control slices. Resorption pits are viewed in a Microphot Fx (Nikon) fluorescence microscope using a polarizing Nikon IGS filter cube. Test dosage results are compared with controls and resulting  $\text{IC}_{50}$  values are determined for each compound tested.

25 The appropriateness of extrapolating data from this assay to mammalian (including human) disease states is supported by the teaching found in Sato, M., et al., Journal of Bone and Mineral Research, Vol. 5, No. 1, pp.31-40, 1990, which is incorporated by reference herein in its entirety. This article teaches that certain  
30 bisphosphonates have been used clinically and appear to be effective in the treatment of Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastases, and bone loss due to immobilization or sex hormone deficiency. These same bisphosphonates are then tested in the resorption pit assay described above to confirm a

correlation between their known utility and positive performance in the assay.

#### EIB ASSAY

- 5                   Duong *et al.*, *J. Bone Miner. Res.*, 8: S378 (1993) describes a system for expressing the human integrin  $\alpha v \beta 3$ . It has been suggested that the integrin stimulates attachment of osteoclasts to bone matrix, since antibodies against the integrin, or RGD-containing molecules, such as echistatin (European Publication 382 451), can effectively block
- 10 bone resorption.

#### Reaction Mixture:

1. 175  $\mu$ l TBS buffer (50 mM Tris•HCl pH 7.2, 150 mM NaCl, 1% BSA, 1 mM  $\text{CaCl}_2$ , 1 mM  $\text{MgCl}_2$ ).
- 15 2. 25  $\mu$ l cell extract (dilute with 100 mM octylglucoside buffer to give 2000 cpm/25  $\mu$ l).
3.  $^{125}\text{I}$ -echistatin (25  $\mu$ l/50,000 cpm) (see EP 382 451).
4. 25  $\mu$ l buffer (total binding) or unlabeled echistatin (non-specific binding).

20                   The reaction mixture was then incubated for 1 h at room temp. The unbound and the bound  $\alpha v \beta 3$  were separated by filtration using a Skatron Cell Harvester. The filters (prewet in 1.5% polyethyleneimine for 10 mins) were then washed with the wash buffer (50

25 mM Tris HCl, 1mM  $\text{CaCl}_2/\text{MgCl}_2$ , pH 7.2). The filter was then counted in a gamma counter.

#### SPA ASSAY

#### 30 MATERIALS:

1. Wheat germ agglutinin Scintillation Proximity Beads (SPA): Amersham
2. Octylglucopyranoside: Calbiochem
- 35 3. HEPES: Calbiochem

4. NaCl: Fisher
5. CaCl<sub>2</sub>: Fisher
6. MgCl<sub>2</sub>: SIGMA
7. Phenylmethylsulfonylfluoride (PMSF): SIGMA
- 5 8. Optiplate: PACKARD
9. Compound A-10 (specific activity 500-1000 Ci/mmol)
10. test compound
11. Purified integrin receptor:  $\alpha_v\beta_3$  was purified from 293 cells overexpressing  $\alpha_v\beta_3$  (Duong *et al.*, *J. Bone Min. Res.*, 8:S378, 1993) according to Pytela (*Methods in Enzymology*, 144:475, 1987)
- 10 12. Binding buffer: 50 mM HEPES, pH 7.8, 100 mM NaCl, 1 mM Ca<sup>2+</sup>/Mg<sup>2+</sup>, 0.5 mM PMSF
13. 50 mM octylglucoside in binding buffer: 50-OG buffer
- 15

#### PROCEDURE:

1. Pretreatment of SPA beads:  
20 500 mg of lyophilized SPA beads were first washed four times with 200 ml of 50-OG buffer and once with 100 ml of binding buffer, and then resuspended in 12.5 ml of binding buffer.
2. Preparation of SPA beads and receptor mixture  
25 In each assay tube, 2.5  $\mu$ l (40 mg/ml) of pretreated beads were suspended in 97.5  $\mu$ l of binding buffer and 20  $\mu$ l of 50-OG buffer. 5  $\mu$ l (~30 ng/ $\mu$ l) of purified receptor was added to the beads in suspension with stirring at room temperature for 30 minutes. The mixture was then centrifuged at 2,500 rpm in a  
30 Beckman GPR Benchtop centrifuge for 10 minutes at 4°C. The pellets were then resuspended in 50  $\mu$ l of binding buffer and 25  $\mu$ l of 50-OG buffer.

3. Reaction

The following were sequentially added into Optiplate in corresponding wells:

- 5 (i) Receptor/beads mixture (75  $\mu$ l)  
(ii) 25  $\mu$ l of each of the following: compound to be tested, binding buffer for total binding or A-8 for non-specific binding (final concentration 1  $\mu$ M)  
10 (iii) A-10 in binding buffer (25  $\mu$ l, final concentration 40 pM)  
(iv) Binding buffer (125  $\mu$ l)  
(v) Each plate was sealed with plate sealer from PACKARD and incubated overnight with rocking at 4°C

15 4. Plates were counted using PACKARD TOPCOUNT

5. % inhibition was calculated as follows:

A = total counts

B = nonspecific counts

20 C = sample counts

% inhibition =  $[(A-B)-(C-B)]/(A-B)/(A-B) \times 100$

### OCFORM ASSAY

Osteoblast-like cells (1.8 cells), originally derived from mouse calvaria, were plated in CORNING 24 well tissue culture plates in  $\alpha$ MEM medium containing ribo- and deoxyribonucleosides, 10% fetal bovine serum and penicillin-streptomycin. Cells were seeded at 40,000/well in the morning. In the afternoon, bone marrow cells were prepared from six week old male Balb/C mice as follows:

30 Mice were sacrificed, tibiae removed and placed in the above medium. The ends were cut off and the marrow was flushed out of the cavity into a tube with a 1 mL syringe with a 27.5 gauge needle. The marrow was suspended by pipetting up and down. The suspension was passed through >100  $\mu$ m nylon cell strainer. The resulting suspension  
35 was centrifuged at 350 x g for seven minutes. The pellet was

resuspended, and a sample was diluted in 2% acetic acid to lyse the red cells. The remaining cells were counted in a hemacytometer. The cells were pelleted and resuspended at  $1 \times 10^6$  cells/mL. 50  $\mu$ L was added to each well of 1.8 cells to yield 50,000 cells/well and 1,25-dihydroxy-vitamin D<sub>3</sub> (D<sub>3</sub>) was added to each well to a final concentration of 10 nM. The cultures were incubated at 37°C in a humidified, 5% CO<sub>2</sub> atmosphere. After 48 h, the medium was changed. 72 h after the addition of bone marrow, test compounds were added with fresh medium containing D<sub>3</sub> to quadruplicate wells. Compounds were added again after 48 h with fresh medium containing D<sub>3</sub>. After an additional 48 h., the medium was removed, cells were fixed with 10% formaldehyde in phosphate-buffered saline for 10 minutes at room temperature, followed by a 1-2 minute treatment with ethanol:acetone (1:1) and air dried. The cells were then stained for tartrate resistant acid phosphatase as follows:

The cells were stained for 10-15 minutes at room temperature with 50 mM acetate buffer, pH 5.0 containing 30 mM sodium tartrate, 0.3 mg/mL Fast Red Violet LB Salt and 0.1 mg/mL Naphthol AS -MX phosphate. After staining, the plates were washed extensively with deionized water and air dried. The number of multinucleated, positive staining cells was counted in each well.

#### $\alpha$ v $\beta$ 5 ATTACHMENT ASSAY

Duong *et al.*, *J. Bone Miner. Res.*, 11: S290 (1996), describes a system for expressing the human  $\alpha$ v $\beta$ 5 integrin receptor.

#### Materials:

1. Media and solutions used in this assay are purchased from BRL/Gibco, except BSA and the chemicals are from Sigma.
2. Attachment medium: HBSS with 1 mg/ml heat-inactivated fatty acid free BSA and 2 mM CaCl<sub>2</sub>.
3. Glucosaminidase substrate solution: 3.75 mM p-nitrophenyl N-acetyl-beta-D-glucosaminide, 0.1 M sodium citrate, 0.25% Triton, pH 5.0.



4. Glycine-EDTA developing solution: 50 mM glycine, 5 mM EDTA, pH 10.5.

Methods:

- 5           1. Plates (96 well, Nunc Maxi Sorp) were coated overnight at 4°C with human vitronectin (3 ug/ml) in 50 mM carbonate buffer (pH 9.6), using 100 µl/well. Plates were then washed 2X with DPBS and blocked with 2% BSA in DPBS for 2h at room temperature. After additional washes (2X) with  
10           DPBS, plates were used for cell attachment assay.
2. 293 (αvβ5) cells were grown in MEM media in presence of 10% fetal calf serum to 90% confluence. Cells were then lifted from dishes with 1X Trypsin/EDTA and washed 3X with serum free MEM. Cells were resuspended in  
15           attachment medium (3 X 10<sup>5</sup> cells/ml).
3. Test compounds were prepared as a series of dilutions at 2X concentrations and added as 50 µl/well. Cell suspension was then added as 50 µl/well. Plates were incubated at 37°C with 5% CO<sub>2</sub> for 1 hour to allow attachment.
- 20           4. Non-adherent cells were removed by gently washing the plates (3X) with DPBS and then incubated with glucosaminidase substrate solution (100 µl/well), overnight at room temperature in the dark. To quantitate cell numbers, standard curve of glucosaminidase activity was  
25           determined for each experiment by adding samples of cell suspension directly to wells containing the enzyme substrate solution.
5. The next day, the reaction was developed by addition of 185 µl/well of glycine/EDTA solution and reading absorbance at  
30           405 nm using a Molecular Devices V-Max plate reader. Average test absorbance values (4 wells per test samples) were calculated. Then, the number of attached cells at each drug concentration was quantitated versus the standard curve of cells using the Softmax program.
- 35

EXAMPLE OF A PHARMACEUTICAL FORMULATION

As a specific embodiment of an oral composition, 100 mg of a compound of the present invention are formulated with sufficient  
5 finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

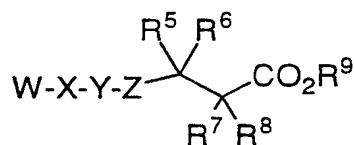
Representative compounds of the present invention were tested and found to bind to human  $\alpha v \beta 3$  integrin. These compounds are generally found to have IC<sub>50</sub> values less than about 100 nM in the SPA  
10 assay.

Representative compounds of the present invention were tested and generally found to inhibit  $\geq 50\%$  the attachment of  $\alpha v \beta 5$  expressing cells to plates coated with vitronectin at concentrations of about 1  $\mu$ M.

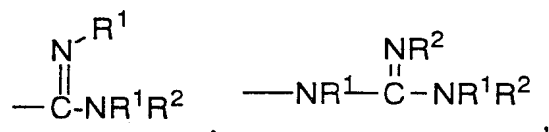
15 While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses  
20 as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for severity of bone disorders caused by resorption, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and  
25 depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended,  
30 therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

## WHAT IS CLAIMED IS:

1. A compound of the formula



- 5 wherein W is selected from the group consisting of



- 10 a 5- or 6-membered monocyclic aromatic or nonaromatic ring system having 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S wherein the ring nitrogen atoms are unsubstituted or substituted with one R<sup>1</sup> substituent and the ring carbon atoms are unsubstituted or substituted with one or two R<sup>1</sup> substituents, and

- 15 a 9- to 14-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system has 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S, and wherein the ring nitrogen atoms are unsubstituted or substituted with one R<sup>1</sup> substituent and the ring carbon atoms are unsubstituted or substituted with one or two R<sup>1</sup> substituents;
- 20

X is selected from the group consisting of

- 25  $-(\text{CH}_2)_v-$ , wherein any methylene (CH<sub>2</sub>) carbon atom is either unsubstituted or substituted with one or two R<sup>1</sup> substituents; and a 5- or 6-membered monocyclic aromatic or nonaromatic ring system having 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S wherein the ring nitrogen atoms are

unsubstituted or substituted with one  $R^1$  substituent and the ring carbon atoms are unsubstituted or substituted with one or two  $R^1$  substituents;

Y is selected from the group consisting of

- 5         $-(CH_2)_m-$ ,
- $-(CH_2)_m-O-(CH_2)_n-$ ,
- $-(CH_2)_m-NR^4-(CH_2)_n-$ ,
- $-(CH_2)_m-S-(CH_2)_n-$ ,
- $-(CH_2)_m-SO-(CH_2)_n-$ ,
- 10        $-(CH_2)_m-SO_2-(CH_2)_n-$ ,
- $-(CH_2)_m-O-(CH_2)_n-O-(CH_2)_p-$ ,
- $-(CH_2)_m-O-(CH_2)_n-NR^4-(CH_2)_p-$ ,
- $-(CH_2)_m-NR^4-(CH_2)_n-NR^4-(CH_2)_p-$ ,
- $-(CH_2)_m-O-(CH_2)_n-S-(CH_2)_p-$ ,
- 15        $-(CH_2)_m-S-(CH_2)_n-S-(CH_2)_p-$ ,
- $-(CH_2)_m-NR^4-(CH_2)_n-S-(CH_2)_p-$ ,
- $-(CH_2)_m-NR^4-(CH_2)_n-O-(CH_2)_p-$ ,
- $-(CH_2)_m-S-(CH_2)_n-O-(CH_2)_p-$ , and
- $-(CH_2)_m-S-(CH_2)_n-NR^4-(CH_2)_p-$ ,

- 20       wherein any methylene ( $CH_2$ ) carbon atom in Y, other than in  $R^4$ , can be substituted by one or two  $R^3$  substituents;

- 25       Z is a 5 membered aromatic or nonaromatic mono- or bicyclic ring system having 0 to 3 heteroatoms selected from the group consisting of N, O, and S, and wherein the ring system is either unsubstituted or substituted with 0, 1, 2, or 3 oxo or thio substituents, and either unsubstituted or substituted with one or more substituents independently selected from the group consisting of  $R^{10}$ ,  $R^{11}$ , and  $R^{12}$ ;

- 30       wherein  $R^1$  and  $R^2$  are each independently selected from the group consisting of

hydrogen, halogen,  $C_{1-10}$  alkyl,  $C_{3-8}$  cycloalkyl,  
 $C_{3-8}$  cycloheteroalkyl,  $C_{3-8}$  cycloalkyl  $C_{1-6}$  alkyl,

C<sub>3-8</sub> cycloheteroalkyl C<sub>1-6</sub> alkyl, aryl, aryl C<sub>1-8</sub> alkyl, amino,  
 amino C<sub>1-8</sub> alkyl, C<sub>1-3</sub> acylamino, C<sub>1-3</sub> acylamino C<sub>1-8</sub> alkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino, (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-8</sub> alkyl,  
 C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkoxy C<sub>1-6</sub> alkyl, hydroxycarbonyl,  
 5 hydroxycarbonyl C<sub>1-6</sub> alkyl, C<sub>1-3</sub> alkoxycarbonyl,  
 C<sub>1-3</sub> alkoxycarbonyl C<sub>1-6</sub> alkyl, hydroxycarbonyl-  
 C<sub>1-6</sub> alkyloxy, hydroxy, hydroxy C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxy-  
 C<sub>1-6</sub> alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy,  
 trifluoroethoxy, C<sub>1-8</sub> alkyl-S(O)<sub>p</sub>, (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 10 C<sub>1-8</sub> alkyloxycarbonylamino, (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyloxy,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>amino, (aryl)<sub>p</sub>amino, aryl C<sub>1-8</sub>  
 alkylsulfonylamino, and C<sub>1-8</sub> alkylsulfonylamino;  
 or two R<sup>1</sup> substituents, when on the same carbon atom, are taken  
 together with the carbon atom to which they are attached to  
 15 form a carbonyl group;

each R<sup>3</sup> is independently selected from the group consisting of  
 hydrogen,  
 aryl,  
 20 C<sub>1-10</sub> alkyl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 25 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 halogen,  
 hydroxyl,  
 oxo,  
 30 trifluoromethyl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxycarbonyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,

- C<sub>1-6</sub> alkylcarbonyloxy,  
 C<sub>3-8</sub> cycloalkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 amino C<sub>1-6</sub> alkyl,  
 5 arylaminocarbonyl,  
 aryl C<sub>1-5</sub> alkylaminocarbonyl,  
 aminocarbonyl,  
 aminocarbonyl C<sub>1-6</sub> alkyl,  
 hydroxycarbonyl,  
 10 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 15 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 20 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkoxy,  
 25 aryl C<sub>1-6</sub> alkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>amino,  
 (aryl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 30 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 arylcarbonyloxy,  
 aryl C<sub>1-6</sub> alkylcarbonyloxy,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>aminocarbonyloxy,  
 C<sub>1-8</sub> alkylsulfonylamino,

- arylsulfonylamino,  
C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
arylsulfonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonylamino,  
5 aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-8</sub> alkoxycarbonylamino,  
C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
aryloxycarbonylamino C<sub>1-8</sub> alkyl,  
aryl C<sub>1-8</sub> alkoxycarbonylamino,  
10 aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonylamino,  
C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
arylcarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonylamino,  
15 aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
aminocarbonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
20 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
25 (aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylsulfonyl,  
C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
30 arylsulfonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonyl,  
aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylcarbonyl,  
C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
35 arylcarbonyl C<sub>1-6</sub> alkyl,

- aryl C<sub>1-6</sub> alkylcarbonyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylthiocarbonylamino,  
 C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 5 arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 10 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl, and  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 or two R<sup>3</sup> substituents, when on the same carbon atom are taken  
 together with the carbon atom to which they are attached to  
 form a carbonyl or a cyclopropyl group,  
 15 wherein any of the alkyl groups of R<sup>3</sup> are either unsubstituted or  
 substituted with one to three R<sup>1</sup> substituents, and provided that each R<sup>3</sup>  
 is selected such that in the resultant compound the carbon atom or  
 atoms to which R<sup>3</sup> is attached is itself attached to no more than one  
 heteroatom;  
 20 each R<sup>4</sup> is independently selected from the group consisting of  
 hydrogen,  
 aryl,  
 aminocarbonyl,  
 25 C<sub>3-8</sub> cycloalkyl,  
 amino C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>aminocarbonyl,  
 (aryl C<sub>1-5</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 30 C<sub>1-8</sub> alkyl,  
 aryl C<sub>1-6</sub> alkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>2-6</sub> alkyl,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>2-6</sub> alkyl,  
 C<sub>1-8</sub> alkylsulfonyl,



- C<sub>1-8</sub> alkoxycarbonyl,  
 aryloxycarbonyl,  
 aryl C<sub>1-8</sub> alkoxycarbonyl,  
 C<sub>1-8</sub> alkylcarbonyl,  
 5 arylcarbonyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 aminosulfonyl,  
 C<sub>1-8</sub> alkylaminosulfonyl,  
 10 (aryl)<sub>p</sub>aminosulfonyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonyl,  
 arylsulfonyl,  
 arylC<sub>1-6</sub> alkylsulfonyl,  
 C<sub>1-6</sub> alkylthiocarbonyl,  
 15 arylthiocarbonyl, and  
 aryl C<sub>1-6</sub> alkylthiocarbonyl,

wherein any of the alkyl groups of R<sup>4</sup> are either unsubstituted or substituted with one to three R<sup>1</sup> substituents;

- 20 R<sup>5</sup> and R<sup>6</sup> are each independently selected from the group consisting of  
 hydrogen,  
 C<sub>1-10</sub> alkyl,  
 aryl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 25 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 30 halogen,  
 hydroxyl,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxycarbonyl,

- (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 C<sub>1-6</sub> alkylcarbonyloxy,  
 C<sub>3-8</sub> cycloalkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 5 amino C<sub>1-6</sub> alkyl,  
 arylaminocarbonyl,  
 aryl C<sub>1-5</sub> alkylaminocarbonyl,  
 aminocarbonyl,  
 aminocarbonyl C<sub>1-6</sub> alkyl,  
 10 hydroxycarbonyl,  
 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 15 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 20 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkoxy,  
 25 aryl C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>amino,  
 (aryl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 30 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 arylcarbonyloxy,  
 aryl C<sub>1-6</sub> alkylcarbonyloxy,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>aminocarbonyloxy,

- C<sub>1-8</sub> alkylsulfonylamino,  
arylsulfonylamino,  
C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
arylsulfonylamino C<sub>1-6</sub> alkyl,  
5 aryl C<sub>1-6</sub> alkylsulfonylamino,  
aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-8</sub> alkoxycarbonylamino,  
C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
aryloxycarbonylamino C<sub>1-8</sub> alkyl,  
10 aryl C<sub>1-8</sub> alkoxycarbonylamino,  
aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonylamino,  
C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
arylcarbonylamino C<sub>1-6</sub> alkyl,  
15 aryl C<sub>1-6</sub> alkylcarbonylamino,  
aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
aminocarbonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
20 (aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
25 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylsulfonyl,  
30 C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
arylsulfonyl C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonyl,  
aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylcarbonyl,

C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 arylcarbonyl C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 5 C<sub>1-6</sub> alkylthiocarbonylamino,  
 C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 10 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl, and  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl;

or R<sup>5</sup> and R<sup>6</sup> are taken together with the carbon atom to which they are  
 15 attached to form an oxo group,  
 wherein any of the alkyl groups of R<sup>5</sup> or R<sup>6</sup> are either unsubstituted or  
 substituted with one to three R<sup>1</sup> substituents,  
 and provided that each R<sup>5</sup> and R<sup>6</sup> are selected such that in the resultant  
 compound the carbon atom to which R<sup>5</sup> and R<sup>6</sup> are attached is itself  
 20 attached to no more than one heteroatom;

R<sup>7</sup> and R<sup>8</sup> are each independently selected from the group consisting of  
 hydrogen,  
 C<sub>1-10</sub> alkyl,  
 25 aryl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 30 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 halogen,  
 hydroxyl,  
 C<sub>1-8</sub> alkylcarbonylamino,

aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxycarbonyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 C<sub>1-6</sub> alkylcarbonyloxy,  
 5 C<sub>3-8</sub> cycloalkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 amino C<sub>1-6</sub> alkyl,  
 arylaminocarbonyl,  
 aryl C<sub>1-5</sub> alkylaminocarbonyl,  
 10 aminocarbonyl,  
 aminocarbonyl C<sub>1-6</sub> alkyl,  
 hydroxycarbonyl,  
 hydroxycarbonyl C<sub>1-6</sub> alkyl,  
 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 15 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 20 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 25 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkoxy,  
 aryl C<sub>1-6</sub> alkyl,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 30 (aryl)<sub>p</sub>amino,  
 (aryl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 arylcarbonyloxy,

- aryl C<sub>1-6</sub> alkylcarbonyloxy,
- (C<sub>1-6</sub> alkyl)<sub>p</sub>aminocarbonyloxy,
- C<sub>1-8</sub> alkylsulfonylamino,
- arylcarbonylamino,
- 5 arylsulfonylamino,
- C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,
- arylsulfonylamino C<sub>1-6</sub> alkyl,
- aryl C<sub>1-6</sub> alkylsulfonylamino,
- aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,
- 10 C<sub>1-8</sub> alkoxycarbonylamino,
- C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,
- aryloxy carbonylamino C<sub>1-8</sub> alkyl,
- aryl C<sub>1-8</sub> alkoxycarbonylamino,
- aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,
- 15 C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,
- arylcarbonylamino C<sub>1-6</sub> alkyl,
- aryl C<sub>1-6</sub> alkylcarbonylamino,
- aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,
- aminocarbonylamino C<sub>1-6</sub> alkyl,
- 20 arylaminocarbonylamino,
- (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,
- (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,
- (aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,
- (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,
- 25 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,
- aminosulfonylamino C<sub>1-6</sub> alkyl,
- (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,
- (C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,
- (aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,
- 30 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,
- (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,
- C<sub>1-6</sub> alkylsulfonyl,
- C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,
- arylsulfonyl C<sub>1-6</sub> alkyl,

- 5 aryl C<sub>1-6</sub> alkylsulfonyl,  
 aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylcarbonyl,  
 C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 arylcarbonyl C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl,  
 aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkylthiocarbonylamino,  
 C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 10 arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
 aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 (aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
 15 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl, and  
 C<sub>7-20</sub> polycyclyl C<sub>0-8</sub> alkyloxycarbonylamino;  
 wherein any of the alkyl groups of R<sup>7</sup> and R<sup>8</sup> are either unsubstituted or  
 substituted with one to three R<sup>1</sup> substituents, and provided that each  
 20 R<sup>7</sup> and R<sup>8</sup> are selected such that in the resultant compound the carbon  
 atom to which R<sup>7</sup> and R<sup>8</sup> are attached is itself attached to no more than  
 one heteroatom;

- 25 R<sup>9</sup> is selected from the group consisting of  
 hydrogen,  
 C<sub>1-8</sub> alkyl,  
 aryl,  
 aryl C<sub>1-8</sub> alkyl,  
 C<sub>1-8</sub> alkylcarbonyloxy C<sub>1-4</sub> alkyl,  
 30 aryl C<sub>1-8</sub> alkylcarbonyloxy C<sub>1-4</sub> alkyl,  
 C<sub>1-8</sub> alkylaminocarbonylmethylene, and  
 C<sub>1-8</sub> dialkylaminocarbonylmethylene;

R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> are each independently selected from the group consisting of

- hydrogen,
- C<sub>1-8</sub> alkyl,
- 5      aryl,
- halogen,
- hydroxyl,
- oxo,
- aminocarbonyl,
- 10      C<sub>3-8</sub> cycloalkyl,
- amino C<sub>1-6</sub> alkyl,
- (aryl)<sub>p</sub>aminocarbonyl,
- hydroxycarbonyl,
- (aryl C<sub>1-5</sub> alkyl)<sub>p</sub>aminocarbonyl,
- 15      hydroxycarbonyl C<sub>1-6</sub> alkyl,
- aryl C<sub>1-6</sub> alkyl,
- (C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,
- (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>2-6</sub> alkyl,
- C<sub>1-8</sub> alkylsulfonyl,
- 20      C<sub>1-8</sub> alkoxycarbonyl,
- aryloxycarbonyl,
- aryl C<sub>1-8</sub> alkoxycarbonyl,
- C<sub>1-8</sub> alkylcarbonyl,
- arylcarbonyl,
- 25      aryl C<sub>1-6</sub> alkylcarbonyl,
- (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,
- aminosulfonyl,
- C<sub>1-8</sub> alkylaminosulfonyl,
- (aryl)<sub>p</sub>aminosulfonyl,
- 30      (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonyl,
- C<sub>1-6</sub> alkylsulfonyl,
- arylsulfonyl,
- aryl C<sub>1-6</sub> alkylsulfonyl,
- aryl C<sub>1-6</sub> alkylcarbonyl,



- C<sub>1-6</sub> alkylthiocarbonyl,  
 arylthiocarbonyl,  
 aryl C<sub>1-6</sub> alkylthiocarbonyl,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-O-(CH<sub>2</sub>)<sub>s</sub>-,  
 5 aryl-(CH<sub>2</sub>)<sub>r</sub>S(O)<sub>p</sub>-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-C(O)-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-C(O)-(CH<sub>2</sub>)<sub>s</sub>-,  
 aryl-(CH<sub>2</sub>)<sub>r</sub>-N(R<sup>4</sup>)-(CH<sub>2</sub>)<sub>s</sub>-,  
 10 HC≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
 15 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>3-7</sub> cycloalkyl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 aryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-CH=CH-(CH<sub>2</sub>)<sub>t</sub>-,  
 20 C<sub>1-6</sub> alkyl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-6</sub> alkylaryl-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 C<sub>1-8</sub> alkylcarbonylamino,  
 aryl C<sub>1-5</sub> alkoxy,  
 C<sub>1-5</sub> alkoxycarbonyl,  
 25 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl,  
 C<sub>1-6</sub> alkylcarbonyloxy,  
 (C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 aminocarbonyl C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkoxy,  
 30 aryl C<sub>1-6</sub> alkoxy,  
 (aryl)<sub>p</sub>amino,  
 (aryl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino,  
 (aryl C<sub>1-6</sub> alkyl)<sub>p</sub>amino C<sub>1-6</sub> alkyl,

arylcarbonyloxy,  
aryl C<sub>1-6</sub> alkylcarbonyloxy,  
(C<sub>1-6</sub> alkyl)paminocarbonyloxy,  
C<sub>1-8</sub> alkylsulfonylamino,  
5 arylsulfonylamino,  
C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
arylsulfonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonylamino,  
aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
10 C<sub>1-8</sub> alkoxycarbonylamino,  
C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
aryloxycarbonylamino C<sub>1-8</sub> alkyl,  
aryl C<sub>1-8</sub>-alkoxycarbonylamino,  
aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
15 C<sub>1-8</sub> alkylcarbonylamino,  
C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
arylcarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonylamino,  
aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
20 aminocarbonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)paminocarbonylamino,  
(C<sub>1-8</sub> alkyl)paminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl)paminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)paminocarbonylamino,  
25 (aryl C<sub>1-8</sub> alkyl)paminocarbonylamino C<sub>1-6</sub> alkyl,  
aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)paminosulfonylamino,  
(C<sub>1-8</sub> alkyl)paminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl)paminosulfonylamino C<sub>1-6</sub> alkyl,  
30 (aryl C<sub>1-8</sub> alkyl)paminosulfonylamino,  
(aryl C<sub>1-8</sub> alkyl)paminosulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylsulfonyl,  
C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
arylsulfonyl C<sub>1-6</sub> alkyl,  
35 aryl C<sub>1-6</sub> alkylsulfonyl,

aryl C<sub>1-6</sub> alkylsulfonyl C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylcarbonyl,  
C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
arylcarbonyl C<sub>1-6</sub> alkyl,  
5 aryl C<sub>1-6</sub> alkylcarbonyl,  
aryl C<sub>1-6</sub> alkylcarbonyl C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylthiocarbonylamino,  
C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
10 aryl C<sub>1-6</sub> alkylthiocarbonylamino,  
aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl, and  
15 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonyl C<sub>1-6</sub> alkyl;  
wherein any of the alkyl groups of R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> are either  
unsubstituted or substituted with one to three R<sup>1</sup> substituents;

wherein  
20 each m is independently an integer from 0 to 6;  
each n is independently an integer from 0 to 6  
each p is independently an integer from 0 to 2;  
each r is independently an integer from 1 to 3;  
25 each s is independently an integer from 0 to 3;  
each t is independently an integer from 0 to 3; and  
v is independently an integer from 0 to 6;

and the pharmaceutically acceptable salts thereof.  
30

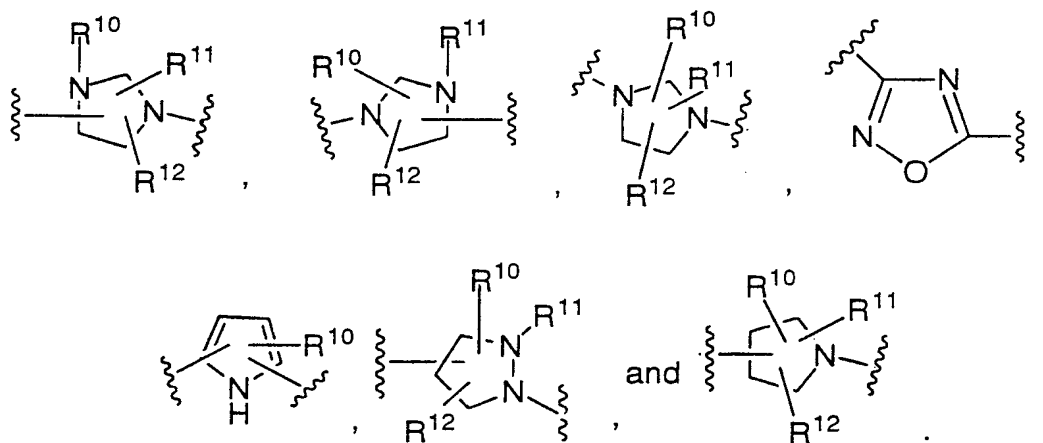
## 2. The compound of Claim 1 wherein

W is

5 a 6-membered monocyclic aromatic ring system having 1 or 2 nitrogen atoms wherein each ring carbon atom is unsubstituted or substituted with one R<sup>1</sup> substituent, or

10 a 9- to 14-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system has 0, 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S, and wherein the ring nitrogen atoms are unsubstituted or substituted with one R<sup>1</sup> substituent and the ring carbon atoms are unsubstituted or substituted with one or two R<sup>1</sup> substituents; and

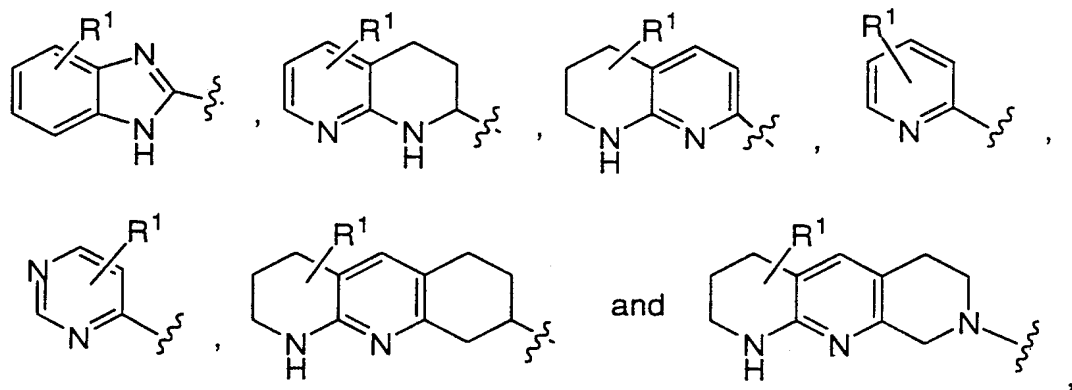
Z is selected from the group consisting of



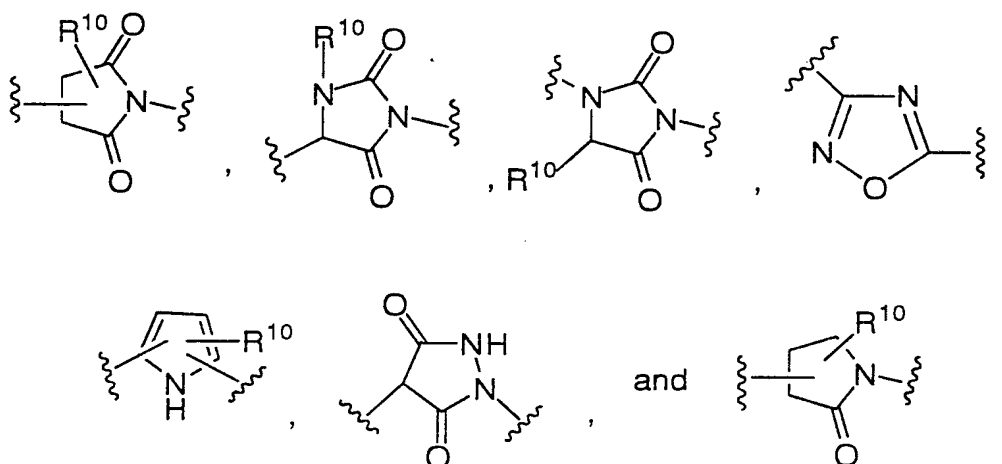
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3. The compound of Claim 2 wherein W is selected from the group consisting of

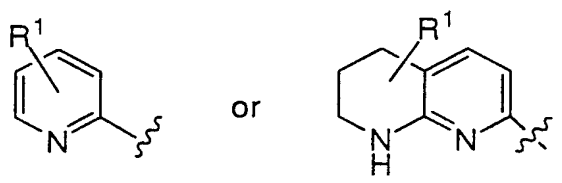


and Z is selected from the group consisting of



5

4. The compound of Claim 3 wherein W is



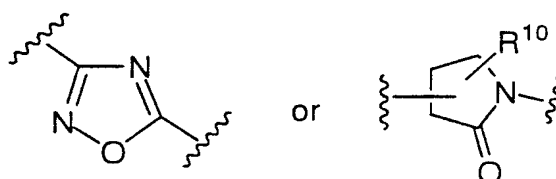
10 X is  $-(CH_2)_v-$ , wherein any methylene (CH<sub>2</sub>) carbon atom is either unsubstituted or substituted with one or two R<sup>1</sup> substituents;

Y is selected from the group consisting of

- 5             $-(CH_2)_m-$ ,  
               $-(CH_2)_m-O-(CH_2)_n-$ ,  
               $-(CH_2)_m-NR^4-(CH_2)_n-$ ,  
               $-(CH_2)_m-S-(CH_2)_n-$ ,  
               $-(CH_2)_m-SO-(CH_2)_n-$ ,  
               $-(CH_2)_m-SO_2-(CH_2)_n-$ ,  
 10            $-(CH_2)_m-O-(CH_2)_n-O-(CH_2)_p-$ ,  
               $-(CH_2)_m-O-(CH_2)_n-NR^4-(CH_2)_p-$ ,  
               $-(CH_2)_m-NR^4-(CH_2)_n-NR^4-(CH_2)_p-$ , and  
               $-(CH_2)_m-NR^4-(CH_2)_n-O-(CH_2)_p-$ ,

15           wherein any carbon atom in Y, other than in  $R^4$ , can be substituted by  
              one or two  $R^3$  substituents;

and Z is



20           5.        The compound of Claim 4 wherein Y is selected from  
              the group consisting of

$(CH_2)_m$ ,  $(CH_2)_m-S-(CH_2)_n$ , and  $(CH_2)_m-NR^4-(CH_2)_n$ ,

25           wherein any carbon atom in Y, other than in  $R^4$ , can be substituted by  
              one or two  $R^3$  substituents, and  
              m and n are integers from 0-3,  
              and v is 0.

6. The compound of Claim 5 wherein each R<sup>3</sup> is independently selected from the group consisting of

hydrogen,  
fluoro,  
5 trifluoromethyl,  
aryl,  
C<sub>1-8</sub> alkyl,  
arylC<sub>1-6</sub> alkyl  
hydroxyl,  
10 oxo,  
arylamino-carbonyl,  
aryl C<sub>1-5</sub> alkylaminocarbonyl,  
aminocarbonyl, and  
aminocarbonyl C<sub>1-6</sub> alkyl; and

15 each R<sup>4</sup> is independently selected from the group consisting of

hydrogen,  
aryl,  
C<sub>3-8</sub> cycloalkyl,  
20 C<sub>1-8</sub> alkyl,  
C<sub>1-8</sub> alkylcarbonyl,  
arylcarbonyl,  
C<sub>1-6</sub> alkylsulfonyl,  
arylsulfonyl,  
25 arylC<sub>1-6</sub>alkylsulfonyl,  
arylC<sub>1-6</sub>alkylcarbonyl,  
C<sub>1-8</sub>alkylaminocarbonyl,  
arylC<sub>1-5</sub>alkylaminocarbonyl,  
arylC<sub>1-8</sub>alkoxycarbonyl, and  
30 C<sub>1-8</sub>alkoxycarbonyl.

7. The compound of Claim 6 wherein R<sup>6</sup>, R<sup>7</sup>, and R<sup>8</sup> are each hydrogen and R<sup>5</sup> is selected from the group consisting of  
hydrogen,

aryl,  
C<sub>1-8</sub> alkyl,  
aryl-C≡C-(CH<sub>2</sub>)<sub>t</sub>-,  
aryl C<sub>1-6</sub> alkyl,  
5 CH<sub>2</sub>=CH-(CH<sub>2</sub>)<sub>t</sub>-, and  
HC≡C-(CH<sub>2</sub>)<sub>t</sub>-.

8. The compound of Claim 7 wherein R<sup>9</sup> is selected from  
the group consisting of hydrogen, methyl, and ethyl.

10

9. The compound of Claim 8 wherein R<sup>9</sup> is hydrogen.

10. The compound of Claim 6 wherein R<sup>5</sup>, R<sup>6</sup>, and R<sup>8</sup> are  
each hydrogen and R<sup>7</sup> is selected from the group consisting of

15

hydrogen,  
aryl,  
C<sub>1-8</sub> alkylcarbonylamino,  
C<sub>1-8</sub> alkylsulfonylamino,  
arylcarbonylamino,  
20 arylsulfonylamino,  
C<sub>1-8</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
arylsulfonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylsulfonylamino,  
aryl C<sub>1-6</sub> alkylsulfonylamino C<sub>1-6</sub> alkyl,  
25 C<sub>1-8</sub> alkoxycarbonylamino,  
C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
aryloxycarbonylamino C<sub>1-8</sub> alkyl,  
aryl C<sub>1-8</sub> alkoxycarbonylamino,  
aryl C<sub>1-8</sub> alkoxycarbonylamino C<sub>1-8</sub> alkyl,  
30 C<sub>1-8</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
arylcarbonylamino C<sub>1-6</sub> alkyl,  
aryl C<sub>1-6</sub> alkylcarbonylamino,  
aryl C<sub>1-6</sub> alkylcarbonylamino C<sub>1-6</sub> alkyl,  
aminocarbonylamino C<sub>1-6</sub> alkyl,  
35 (C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,



(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
arylaminocarbonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
5 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino C<sub>1-6</sub> alkyl,  
aminosulfonylamino C<sub>1-6</sub> alkyl,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
(aryl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
10 (aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylthiocarbonylamino,  
C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl,  
arylthiocarbonylamino C<sub>1-6</sub> alkyl,  
15 aryl C<sub>1-6</sub> alkylthiocarbonylamino, and  
aryl C<sub>1-6</sub> alkylthiocarbonylamino C<sub>1-6</sub> alkyl.

11. The compound of Claim 10 wherein R<sup>7</sup> is selected  
from the group consisting of  
20 hydrogen,  
aryl,  
C<sub>1-8</sub> alkylcarbonylamino,  
aryl C<sub>1-6</sub> alkylcarbonylamino,  
arylcarbonylamino,  
25 C<sub>1-8</sub> alkylsulfonylamino,  
aryl C<sub>1-6</sub> alkylsulfonylamino,  
arylsulfonylamino,  
C<sub>1-8</sub> alkoxycarbonylamino,  
aryl C<sub>1-8</sub> alkoxycarbonylamino,  
30 arylaminocarbonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminocarbonylamino,  
(C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino, and  
(aryl C<sub>1-8</sub> alkyl)<sub>p</sub>aminosulfonylamino.

12. The compound of Claim 11 wherein R<sup>9</sup> is selected from the group consisting of hydrogen, methyl, and ethyl.
13. The compound of Claim 12 wherein R<sup>9</sup> is  
5 hydrogen.
14. The compound of Claim 6 selected from the group consisting of
  - 10 Ethyl 3(S)-(3-fluorophenyl)-3-[2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthydin-2-yl)-propyl]-pyrrolidin-1-yl]-propionate;
  - Ethyl 3(S)-(3-fluorophenyl)-3-[2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthydin-2-yl)-propyl]-pyrrolidin-1-yl]-propionate;
  - 15 Ethyl 3(S)-(2,3-dihydro-benzofuran-6-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionate;
  - Ethyl 3(S)-(2,3-dihydro-benzofuran-6-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionate;
  - 20 Ethyl 3(S)-(quinolin-3-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionate;
  - 25 Ethyl 3(S)-(quinolin-3-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionate;
  - 3(S)-(3-Fluorophenyl)-3-[2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthydin-2-yl)-propyl]-pyrrolidin-1-yl]-propionic acid;
  - 30 3(S)-(3-Fluorophenyl)-3-[2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthydin-2-yl)-propyl]-pyrrolidin-1-yl]-propionic acid;

- 3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 5 3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(Quinolin-3-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 10 3(S)-(Quinolin-3-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 2(S)-Benzenesulfonylamino-3-[3-(3-[1,8]naphthyridin-2-yl)-propyl]-[1,2,4]oxadiazol-5-yl)-propionic acid;
- 15 3(S)-(6-Ethoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(6-Amino-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 20 3(S)-(4-Methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 25 3-(6-Methylamino-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(2-Fluoro-biphenyl-4-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 30 3(S)-(2-Oxo-2,3-dihydro-benzoxazol-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

- 3(S)-(4-Ethoxy-3-fluorophenyl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 5 3(S)-(5-Ethoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(5-Methoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 10 3(S)-(Ethynyl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(6-Methoxy-pyridin-3-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 15 3(S)-(2-Oxo-2,3-dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 20 3(S)-(2,3-Dihydro-1H-4-oxa-1,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 25 3(S)-(2-Oxo-3,4-dihydro-2H-1-oxa-4,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 30 3(S)-(3,4-Dihydro-2H-1-oxa-4,5-diaza-naphthalen-7-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3-(Furo-[2,3-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

- 3-(2,3-Dihydrofuro[2,3-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 5 3-(Furo-[3,2-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3-(2,3-Dihydrofuro[3,2-b]pyridin-6-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 10 3(S)-(Benzimidazol-2-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(1H-Imidazo[4,5-c]pyridin-2-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 15 3(S)-(Benzoxazol-2-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 3(S)-(1-Methyl-1H-pyrazol-4-yl)-3-(2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;
- 20 3(S)-{2-oxo-3-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl}-pent-4-enoic acid;
- 25 and the pharmaceutically acceptable salts thereof.

15. The compound of Claim 14 selected from the group consisting of

- 30 3(S)-(3-Fluorophenyl)-3-[2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl]-propionic acid;
- 3(S)-(3-Fluorophenyl)-3-[2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl]-propionic acid;
- 35

3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

5 3(S)-(2,3-Dihydro-benzofuran-6-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

3(S)-(Quinolin-3-yl)-3-(2-oxo-3(R)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

10 3(S)-(Quinolin-3-yl)-3-(2-oxo-3(S)-[3-(5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-propyl]-pyrrolidin-1-yl)-propionic acid;

and the pharmaceutically acceptable salts thereof.

15 16. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

20 17. A pharmaceutical composition made by combining a compound according to Claim 1 and a pharmaceutically acceptable carrier.

25 18. A process for making a pharmaceutical composition comprising combining a compound according to Claim 1 and a pharmaceutically acceptable carrier.

19. The composition of Claim 16 which further comprises an active ingredient selected from the group consisting of

- 30 a) an organic bisphosphonate or a pharmaceutically acceptable salt or ester thereof,  
b) an estrogen receptor modulator,  
c) a cytotoxic/antiproliferative agent,  
d) a matrix metalloproteinase inhibitor,  
35 e) an inhibitor of epidermal-derived, fibroblast-derived, or platelet-derived growth factors,

- 5
- f) an inhibitor of VEGF,
  - g) an inhibitor of Flk-1/KDR, Flt-1, Tck/Tie-2, or Tie-1,
  - h) a cathepsin K inhibitor; and
  - i) a prenylation inhibitor, such as a farnesyl transferase inhibitor or a geranylgeranyl transferase inhibitor or a dual farnesyl/geranylgeranyl transferase inhibitor; and mixtures thereof.

- 10
20. The composition of Claim 19 wherein said active ingredient is selected from the group consisting of
- a.) an organic bisphosphonate or a pharmaceutically acceptable salt or ester thereof,
  - b.) an estrogen receptor modulator, and
  - c. a cathepsin K inhibitor;
- 15
- and mixtures thereof.

- 20
21. The composition of Claim 20 wherein said organic bisphosphonate or pharmaceutically acceptable salt or ester thereof is alendronate monosodium trihydrate.

- 20
22. The composition of Claim 19 wherein said active ingredient is selected from the group consisting of
- a.) a cytotoxic/antiproliferative agent,
  - b.) a matrix metalloproteinase inhibitor,
  - 25 c.) an inhibitor of epidermal-derived, fibroblast-derived, or platelet-derived growth factors,
  - d.) an inhibitor of VEGF, and
  - e.) an inhibitor of Flk-1/KDR, Flt-1, Tck/Tie-2, or Tie-1; and mixtures thereof.
- 30

- 30
23. A method of eliciting an integrin receptor antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1.
- 35

24. The method of Claim 23 wherein the integrin receptor antagonizing effect is an  $\alpha v\beta 3$  antagonizing effect.

25. The method of Claim 24 wherein the  $\alpha v\beta 3$  antagonizing effect is selected from the group consisting of inhibition of bone resorption, restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, viral disease, and tumor growth.

26. The method of Claim 25 wherein the  $\alpha v\beta 3$  antagonizing effect is the inhibition of bone resorption.

27. The method of Claim 23 wherein the integrin receptor antagonizing effect is an  $\alpha v\beta 5$  antagonizing effect.

28. The method of Claim 27 wherein the  $\alpha v\beta 5$  antagonizing effect is selected from the group consisting of inhibition of restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, and tumor growth.

29. The method of Claim 23 wherein the integrin receptor antagonizing effect is a dual  $\alpha v\beta 3/\alpha v\beta 5$  antagonizing effect.

30. The method of Claim 29 wherein the dual  $\alpha v\beta 3/\alpha v\beta 5$  antagonizing effect is selected from the group consisting of inhibition of bone resorption, restenosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, viral disease, and tumor growth.

31. The method of Claim 23 wherein the integrin antagonizing effect is an  $\alpha v\beta 6$  antagonizing effect.

32. The method of Claim 31 wherein the  $\alpha v\beta 6$  antagonizing effect is selected from the group consisting of angiogenesis, inflammatory response, and wound healing.



33. A method of eliciting an integrin receptor antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 16.

5

34. A method of treating or preventing a condition mediated by antagonism of an integrin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 16.

10

35. A method of inhibiting bone resorption in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 16.

15

36. A method of inhibiting bone resorption in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 20.

20

37. A method of treating tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 22.

25

38. A method of treating tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1 in combination with radiation therapy.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/26539

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :A61K 31/435, 31/40; C07D 207/26, 413/06, 471/04, 401/06  
US CL :546/122, 269.1, 278.4; 548/550, 551; 514/300, 340, 343, 424

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/122, 269.1; 548/551; 514/300, 424

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN-FILE REGISTRY - structure search

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REGISTRY FILE, STN, CHEMICAL ABSTRACTS, 127:121652, OKAYAMA et al., 'Preparation of beta-(3-guanidopropyl)-beta-(arylsulfonylamino) lactam derivatives having specific thrombin-inhibitory activity', Chem. Abstr., Vol. 127, abstract no. 121652, (1997) Japanese Kokai Tokkyo Koho 09-165370, June 1997, see entire abstract and compound.	1 and 16-18
X	REGISTRY FILE, STN, CHEMICAL ABSTRACTS, 123:33068, BOVY et al., 'Preparation of [(aminoiminomethyl) phenyl] imidazolones and related compounds as platelet aggregation inhibitors; Chem. Abstr., Vol. 123, abstract no. 33068 (1995) WO 9506038 A1, 02 March 1995, see the 2 compounds shown which are intermediates.	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

16 FEBRUARY 1999

Date of mailing of the international search report

9 8 MAR 1999

Name and mailing address of the ISA/US  
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/26539

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:  
1, 2 and 16-38 in part and claims 3-15
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/26539

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

- I Claims 1-38, cpds. and pharmaceutical compositions and methods where W is heterocyclic and Z is heterocyclic.
- II Claims 1 and 16-38 cpds. and pharmaceutical compositions and methods where W is heterocyclic and Z is not heterocyclic.
- III Claims 1, 2 and 16-38 cpds. where W is carbocyclic and Z is heterocyclic.
- IV Claims 1 and 16-38 cpds. where W is carbocyclic and Z is not heterocyclic.
- V Claims 1 and 16-38 involving compounds where W is amidino and Z is heterocyclic.
- VI Claims 1 and 16-38 involving compounds where W is amidino and Z is not heterocyclic.
- VII Claims 1 and 16-38 involving compounds where W is guanidino and Z is heterocyclic.
- VIII Claims 1 and 16-38 involving compounds where W is guanidino and Z is not heterocyclic.